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(54) Title: INDIVIDUAL CALIBRATION OF BLOOD GLUCOSE FOR SUPPORTING NONINVASIVE SELF-MONITORING BLOOD GLUCOSE

(57) Abstract

A method is provided for calibrating a noninvasive glucose monitor for prospective noninvasive glucose determination. Spectroscopic transflectance readings are measured on the patient's skin using a noninvasive glucose monitor. The patient's blood glucose level is measured with an invasive glucose monitor. The noninvasive and invasive measurements are correlated to form an individual algorithm for each patient. Preferably, the position of the patient's skin with respect to the probe of the noninvasive monitor is spatially adjusted while collecting the transflectance measurements such that multiple readings are taken on the patient's skin. The measurements are preferably taken over a period of time and over a plurality of glucose levels in the patient.

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INDIVIDUAL CALIBRATION OF BLOOD GLUCOSE FOR SUPPORTING NONINVASIVE SELF-MONITORING BLOOD GLUCOSE

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a process of calibrating a noninvasive blood glucose sensing monitor. In this invention, a process for calibrating a blood glucose monitor for an individual patient is described. This process provides a means for achieving the exquisite control or management of both signal as well as noise within the noninvasive measurement during calibration and subsequently during the long-term use of the calibrated device by humans desiring to monitor their level of blood glucose on demand.

2. Background Art

U.S. Patent Nos. 5,070,874; 5,360,004; 5,379,764; 5,471,981; and 5,460,177 describe methods for the noninvasive measurement of blood glucose levels. In general, these methods use a spectrophotometer to measure the absorbance of near-infrared radiation at different wavelengths across the range of interest. The absorbance plotted against the wavelengths constitutes a spectrum. By analyzing the spectrum, the blood glucose levels, or changes thereto, can be determined. As the blood glucose levels vary, the detected spectrum also changes.

It is generally known that calibration of analytical devices can be accomplished through using univariate or multivariate mathematical/statistical analysis methodology. As such, reports of noninvasive blood glucose sensing have demonstrated the correlation of measurements of spectroscopic measurements obtained noninvasively with an alternative method known as a reference method requiring invasive and often painful sample collection. While much previous work deals with the process of calibration leading to interesting mathematical/statistical correlations, mathematical models have not yet been shown to be useful for reliable

prospective glucose tests of a diabetic patient's blood glucose.

Previous reports on noninvasive glucose sensing have not proven that prospective noninvasive glucose determinations using these methods possess sufficient accuracy to allow the newly emerging technology to serve as a replacement of older invasive technology. By "prospective" testing, we mean that the glucose test results are followed forward in time, allowing evaluation of long-term accuracy. Prospective testing involves evaluation and continuous monitoring of independent glucose tests as additional time lapses after first establishing the calibration. Previous reports have not demonstrated that the noninvasive technology can maintain model stability to the extent that these independent test results can remain accurate even as time elapses after the initial creation of the calibration model.

In previous calibration methods, data from numerous patients has been collected to calibrate a glucose monitor to a theoretical "norm". Test results from an individual patient were then compared to this norm to try to calculate that individual patient's glucose level. However, calibration using data obtained from a multitude of patients to prospectively measure glucose in any one patient has not been successful. This is mainly due to the large person-to-person variation in the morphology, physiology and chemistry of the skin.

Therefore, it is an object of the invention to provide a method of individually calibrating a noninvasive blood glucose sensing device to overcome the problems associated with patient-to-patient variability and also variability with an individual patient. It is also an object of the invention to provide a personalized calibration method that spans a patient's skin, spans time between readings and spans glucose variation inherent in a diabetic condition.

SUMMARY OF THE INVENTION

A method is provided for calibrating a noninvasive glucose monitor for prospective noninvasive glucose determination. Spectroscopic transflectance readings are measured on the patient's skin using a noninvasive glucose monitor. The patient's blood glucose level is measured with an invasive glucose monitor. The noninvasive and invasive measurements are correlated to form an individual algorithm for each patient.

Preferably, the position of the patient's skin with respect to the probe of the noninvasive monitor is spatially adjusted while collecting the transflectance measurements such that multiple readings are taken on the patient's skin. The measurements are preferably taken over a period of time and over a plurality of glucose levels in the patient.

A complete understanding of the invention will be obtained from the following description when taken in connection with the accompanying drawing figures.

DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a plot of a skin movement pattern for noninvasive data collection. In this plot, the skin movement over a stationary probe is indicated. A heavy bar represents an instance when the probe collects replicate readings at a fixed position on the skin. The term "replicate readings" means that the monitor took skin spectra repeatedly without moving the arm;

Fig. 2 is a plot of temporal history during multi-epoch calibration. In this plot the reference method reading (YSI) vs. time plot is shown. The points were taken in such a way as to provide low correlation of glucose ($R<0.5$) with environmental sensors. Sensors include temperature, humidity and barometric pressure. The correlation coefficient is calculated in the manner of the Pearson correlation coefficient;

Fig. 3 is a plot of performance without spatio-temporal adaptation;

Fig. 4 is a plot showing the improved results after using spatio-temporal adaptation;

Figs. 5A-5F are flow diagrams showing a patient calibration procedure. In these flow diagrams, the process of data collection for calibration, verification and skin library development is shown. The skin library contains the patient's calibration algorithm, information about the control material and reference material. The prediction process makes use of the skin library to generate a patient's glucose test result;

Figs. 6A and 6B show flow diagrams for collecting measurement data using a noninvasive monitor having a memory (PCMCIA) card. In order to demonstrate that the calibration can be used by a patient, the prediction of independent data should produce accurate and precise glucose test results. The prediction flow diagrams describe the use of the skin library components which are used in subsequent calculations leading to a glucose test result; and

Figs. 7A-7C show flow diagrams for a noninvasive glucose monitor acquisition session.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

It is to be understood that the invention may assume various alternative variations and step sequences, except where expressly specified to the contrary. It is also to be understood that the specific devices and processes described in the attached drawings and the following specification are simply exemplary embodiments of the invention. Hence, specific time periods and other parameters related to the embodiments disclosed herein are not to be considered as limiting.

The present application pertains to the manner in which the data is collected to support an individual calibration for a noninvasive blood glucose monitor used by a particular patient. Only through careful calibration with and for each individual patient is it possible to achieve the accuracy and precision for prospective self-

monitoring of blood glucose with a noninvasive monitor. Careful calibration involves managing three sources of variation: 1) patient-to-patient variation as previously described; 2) spatial variation arising from the heterogeneous nature of the skin within an individual patient; and 3) time-based variation that occurs as the patient undergoes changes in the biology of the cellular skin media or as the monitor device undergoes minute, diminutive changes in illumination signal strength, detector fluctuation and optical variation.

The noninvasive sensing of patient glucose variation depends on effective management of nuisance variation from these several sources. Since it is not practical to entirely eliminate all sources of variation, it is therefore necessary to manage nuisance variation judiciously. In this way, one can decrease the effect of nuisance variance when measuring glucose variation. The present invention accomplishes this by performing measurements controlled in both space and time.

The significant patient-to-patient variation prevalent in the prior art systems is made irrelevant by confining the calibration of the device to an individual patient. That is, for each patient who would use the device, a unique algorithm related to the measured response to glucose is determined from data obtained only from that patient.

Spatial adjustment referred to here occurs as motion is applied so that a relatively large area of the patient's skin is monitored, preferably through the use of an arm motion mechanism. The patient's arm is spatially adjusted with respect to the probe. However, similar adjustment may be realized by spatially adjusting the emitted light beam, whether or not through a probe, across the patient's skin. In addition, a larger area of the patient's arm can be illuminated, preferably simultaneously, with the light beam and multiple readings

can be taken over this area while moving neither the probe(s) nor the patient's arm.

Temporal adjustment occurs as the patient continues to use the device during a multi-epoch period. An "epoch" refers to a period during which measurements occur, such as a calendar day. Multi-epoch measurements occur as the patient continues to make repeated readings on a daily basis over several days.

In accordance with the present invention, the patient's skin is measured with a noninvasive, infrared spectrometer. At the same time that these measurements are performed, the patient's blood glucose is measured with a highly accurate invasive method which is relied upon to yield a reference measurement of the patient's blood glucose. The mathematical correlation of the two measurements gives rise to an algorithm for that patient that can be used to provide an output consisting of a glucose reading by using an input to the mathematical equation consisting of the patient's spectroscopic measurement or spectrum.

The spectroscopic readings of the patient's skin are converted into glucose levels by using the patient's individual algorithm which relates future spectroscopic readings of the patient's skin to an associated glucose level. The conversion of spectral information into glucose concentration information is possible through using the mathematical algorithm previously determined as part of the calibration process. As the skin of a diabetic patient undergoes changes in glucose levels, i.e., as the patient's blood glucose level changes, the patient's spectroscopic measurements provide a fingerprint of the spectral characteristics during any specific time when a patient's glucose is at a new glucose level.

This invention pertains to the process of collecting sufficient data to support the successful calibration of an individual patient for self-monitoring of blood glucose with a noninvasive monitor. The data is

considered to be sufficient after (a) satisfying a statistical sample size criterion and (b) achieving low correlation of glucose, as determined by the reference glucose determination method, with environmental sensors.

The method uses a two-epoch calibration system as a means for screening whether a patient can be calibrated. The first epoch is designed to provide calibration data. The second epoch is designed to provide verification data, whereby the data is used to verify whether the patient's individual calibration possesses the capability of providing accurate predictions of the patient's self-monitored blood glucose. In this way unsuccessful calibrations are screened out.

Turning to the data collection, the monitor uses a programmable skin movement pattern, an example of which is shown in Fig. 1, that can be adjusted to an individual patient's skin variation. The skin variation is determined by the mean and standard deviation of the skin spectra as a function of skin movement as described hereinbelow. The dithering field shown in Fig. 1 has a length of about 3.5 inches. Sampling over the dithering field helps compensate for the heterogeneity of the sampling medium.

The action of arm motion, while performing the process of individual calibration, provides a means of managing, or providing control over, spectral variability encountered when measuring the heterogeneous sample of the patient. Sampling variability can be described statistically by estimating the standard deviation spectrum from the arm measurement. The sample variance can be described as $s^2 = \Sigma(X-Xbar)^2/n-1$, where X is a vector measurement of the spectrum of the patient's skin transflectance and Xbar is the mean spectrum of n spectra taken to provide a test result. The magnitude of n can be determined by calculating the sample size in the manner described hereinafter. The pattern of movements effected on the arm consists of repeated short and long dither movements which are made in sequence when the device is in

operation. Although the pattern is shown in Fig. 1 as having a specific pattern, this pattern may vary from time to time as the patient's skin undergoes changes. A successful readout is possible only if spatial adjustments are deployed on the patient's arm. This is due to the necessity of achieving a proper balance of sampling variability prior to rendering a patient's glucose readout. Further, the arm movement pattern is adjustable and can be optimized for each patient. As an example, bars of variable width are shown in Fig. 1. The width of the bar is proportional to the degree to which the sample has been replicated, i.e., that the arm has been repeatedly measured without moving the arm to a new location within the dithering field. As new measurements are made, each measurement must meet an acceptance criteria of goodness-of-fit before replication can proceed. If the goodness-of-fit criteria is met, then the process of replication proceeds. Goodness-of-fit can be accomplished by a number of acceptable methods, such as calculating the Euclidean or mahalanobis distance relative to previous skin measurements, vector correlation, or through use of linear discriminant analysis or use of lack-of-fit statistical analysis. The number of replicates increases until achieving no additional improvement in the sampling variance or until reaching a practical limit. The number of replicates and searching of new skin sites within the dithering field are a function of speed, which may vary as new hardware and software are tested.

After successful completion of the two-epoch calibration, the method uses a multi-epoch period of calibration data collection, which is necessary for collecting sufficient information for building a calibration that can predict a patient's blood glucose during in-home use, whereby the patient is making use of the monitor in their own home. A sufficient quantity is predetermined by calculating sample sizes for within- and between-day variation in skin spectral responses.

As an example of how temporal adjustments are made, Fig. 2 illustrates how the adjustment of the glucose levels is performed over time. The y-axis shows the patient's blood glucose as determined by a highly accurate laboratory method, such as a Yellow Springs Instruments Blood Glucose Analyzer (YSI). This method makes use of the action of the glucose oxidase enzymatic reaction with the glucose molecules within the whole blood sample of the patient's blood, which then produces a read-out in glucose concentration having the units of mg/dL glucose. This value has an accuracy of <5% error {error=(actual-predicted)/actual*100} in the YSI concentration over the clinical range of the patient's calibration of <100 to >400 mg/dL. The x-axis shows the date/time index that has elapsed from the beginning of the calibration period. As an example, the x-axis index is a simple running index starting at 0 and counting upward, as time elapses from date/time = 0 to date/time = 650 (30 days). The maximum value on the x-axis in Fig. 2 corresponds to 30 days of data collection. For each patient the number of days may vary. The time period over which the time must elapse is determined by performing the calculation of statistical sample size discussed hereinafter. The sample size requires that the day-to-day variation is used in estimating the number of days required for calibration, where the number of days to be included in the calibration serves as a guide but may not need to be rigidly followed. The number of days required in the calibration data collection depends on the patient's daily variation throughout calibration. Usually, a successful calibration must span several days of variation to allow for daily variation, assumed to be prototypical of the patient's future, to occur and then allow for more robust model building.

Within Fig. 2, the placement of the YSI levels is chosen such that the YSI covariate is not significantly correlated with any of the environmental sensor covariates

which are located within the noninvasive glucose case. The statistical model, which is used to test YSI and sensor covariates as being statistically insignificant, follows the form: $S=YB+E$, where S is the vector of sensor readings, Y is a vector of YSI readings, B is a vector of regression coefficients, and E is the unexplained variation within the model. The environmental sensors include: 1) ambient temperature, 2) probe temperature, 3) spectrograph temperature, 4) lamp temperature, 5) detector temperature, 6) ambient humidity and 7) barometric pressure. As data is collected from date/time = 0, the YSI vs. environmental sensor correlation is continually updated until meeting the following criteria: a) an appropriate sample size is met and b) the sensor correlation is $r<0.5$ (r = Pearson correlation coefficient).

The calibration process typically involves two days of testing in a calibration center followed by several weeks of testing in the patient's home. The frequency of the readings during the two-day calibration, as well as the timing of the daily readings, is discussed below.

The monitor for implementation of this method preferably uses a programmable time sequence adjustable and adapted to the patient's changing spectroscopic skin readings as changes occur over time. The number of the patient's skin readings over time is adjusted after determining the between-day variation. The between-day variation is determined by calculating the mean and standard deviation of spectra over about two to seven days.

The use of adjustable spatial as well as temporal, i.e., spatio-temporal adjustments, allows for building a calibration for individuals. When using spatio-temporal adjustment during an individual calibration for each patient, the test results of noninvasive glucose readings are improved (Figs. 3 and 4).

Thus, the present invention provides a method of collecting data from two devices of measure that provide paired measurements: i) measurements of the spectroscopic

transflectance of a patient's skin and ii) measurements of a patient's blood glucose. The purpose of this is to provide a sufficient data set that can lead to a mathematical relationship supporting a self-monitored blood glucose test capability for an individual. The spectroscopic measurements are performed by a noninvasive blood glucose analyzer. The blood glucose analyzer will provide blood glucose levels having an accuracy of less than 5% error when compared to a laboratory method. The blood glucose analyzer is considered as a "reference" measurement of the true blood glucose value, and renders <5% error over a range of blood glucose from about 50 mg/dL to 400 mg/dL. Paired, longitudinal data is collected as the patient's blood is measured simultaneously with spectral data collection, preferably during a two-epoch period, to support an individual calibration for self-monitored blood glucose. The first of these epochs, such as is possible on the first of two days, is used to calibrate the monitor. The process of collecting the calibration data is described in Figs. 5 and 7. The data is classified into a plurality of clusters of which each possesses a high degree of similarity of spectra assigned to a specific cluster. The relative spectral dissimilarity between clusters is large compared to similarity within a cluster. One or many clusters are used to describe prototypically acceptable or unacceptable data. The Euclidean distance between cluster centroids defining acceptable versus unacceptable ranges between about 0.5 to 1.5 Euclidean distance. A multivariate calibration is completed by using ordinary least squares, principal component regression or any other multivariate analysis technique to derive an equation of the form:

$$Y=XB + e$$

where Y is a vector of predicted glucose values, X is an n by m matrix of spectral responses, where n is the number of test results and m is the number of spectral variables, and

B is a vector of least squares coefficients and e is a vector of errors.

The second of the two epochs, such as can be collected on the second consecutive day of two days, is used to verify the monitor. The procedure used to verify the predictive capability of the calibration is known as prediction and is shown in Fig. 6. The number of readings during these epochs shall be determined by a sample size determination criterion such as the following equation or any equation following the form:

$$N_{single\text{-}epoch} \geq Z\sigma/L$$

where N is the number of readings during the calibration. The number of spectroscopic measurements on the skin preferably meets or exceeds the value of N indicated in the above formula. The value of Z is approximated by the standard normal statistic. The variable σ is the measurement of the variation which represents the patient's skin variation. L is the value relating the desired clinical accuracy of the patient's skin variation.

A sample is collected to provide at least N measurements at each point in time that a patient's skin is adjusted to a new level of glucose. A new level of glucose is preferably achieved at such a rate of change as to provide enough time to acquire at least N measurements within a given glucose level. The glucose level associated with the N samples or measurements defines a discrete level of glucose that can be mathematically coupled to the state of the skin at a particular glucose concentration. The term "level" refers to an independent level of the patient's blood glucose which has been associated with an appropriate amount of spectroscopic samples of the patient's skin. A successful spectroscopic measurement will require sufficient signal to noise ratio, which can be achieved by striving for a high level of statistical power as to provide a representative sample of the patient's skin. Typically, the sample size supporting accurate glucose readings requires α=0.05 and β=0.1.

The patient's skin variation is determined by deploying a skin movement mechanism on the patient's skin while simultaneously collecting the patient's spectroscopic transflectance measurements. The patient's skin variation is initially evaluated by determining the Pearson correlation coefficient "r" of the patient's newly acquired skin measurement with that of a previously determined skin spectrum. The previous skin measurement can be estimated from the training data by calculating the sample standard deviation in the manner previously described. Rules for skin movement are as follows: (1) only those skin readings passing $r>0.95$ are collected and stored in the memory of the monitor; (2) skin measurements having $r<0.95$ are followed by a large skin movement jump and do not require replicated measurements; (3) skin measurements having $r>0.95$ are replicated while continuing to monitor the value of r for each new measurement and recursively updating the estimate of the variance of the replicated measurements; and (4) replication ceases when the variance does not continue to improve or when reaching a time and/or memory limit.

The present process of calibration is preferably based on two-epoch adjustments of a patient's glucose, whereby adjustments are made by the usual means of therapy prescribed by the patient's physician. Increased blood glucose will be achieved by using a clinically acceptable method, such as the method of oral glucose loading, whereby the patient ingests a quantity of glucose such as needed to increase the patient's blood glucose level. The patient's glucose will be adjusted downward by an acceptable method of insulin therapy consistent with the patient's usual physician prescribed insulin therapy. The insulin therapy results in a downward adjustment in the patient's blood glucose. The patient's glucose excursion is defined as the difference between the highest and lowest level achieved during the calibration. The patient's glucose excursion

preferably should exceed 200 mg/dL during the calibration process.

A diabetic's calibration algorithm is verified by testing the capability of the patient's individual algorithm to provide an accurate and precise reading of the patient's blood glucose test results from the patient on newly acquired data during the second epoch. Prediction frequency is preferably determined as prediction frequency = test results/attempts to obtain a test result * 100%. Acceptable accuracy, precision and prediction frequency are as follows: accuracy and precision should support a standard error of prediction <30 mg/dL standard error for independent predictions over a period of time that the diabetic patient or patient's physician expects to use the monitor. Prediction frequency should be between 50-100%. Satisfactory accuracy, precision and prediction frequency performance are dependent on achieving the successful individual calibration; improvements in performance are possible by using multi-epoch calibrations. The number of epochs included in the multi-epoch calibration is determined in the same manner as the single-epoch expression. In the same way as with a single epoch, the value of σ must be estimated. However, in this case it shall be an estimate of the between-day variation. Between-day variation shall be determined by performing measurements over several days (preferably ranging from a minimum of about three to as many as about seven days). The statistical estimates of the mean and standard deviation of the daily variation are used in a sample size determination, which is used to determine the duration of time over which the patient's spectral and blood glucose paired readings are performed. The sample size for the patient's temporal readings is determined by the following equation or by any equation having the form:

$$N_{multi\text{-}epoch} = Z\sigma/L$$

As a diagnostic evaluation of the quality of the calibration data, the correlation between glucose levels

and environmental factors is determined. In the patient's multi-epoch data, the glucose variation is not correlated with the ambient temperature, skin temperature, internal temperature for any device internal-temperature sensor, or relative humidity and barometric pressure. In each case a correlation of $r<0.5$ is preferably determined for each sensor, where "r" is the Pearson correlation coefficient showing glucose correlation with the above-mentioned environmental sensors. When finding that the blood glucose reference values are correlated with any of the environmental sensors, yielding $r>0.5$, then additional data must be added to the patient's multi-epoch calibration such that the correlation coefficient can be driven to a level $r<0.5$.

EXAMPLE CALCULATIONS

Figs. 5-7 describe how data is collected and evaluated. While different analytical methods may be employed, the following are example mathematical analysis methods for the steps described in Figs. 5-7:

Skin Level Threshold Check

The purpose of the skin level threshold check is to detect an open probe in the noninvasive monitor. For each skin spectra, the skin level threshold check is performed as follows:

1. Using a selected pixel, for example, pixel 13, compute a normalized floating-point pixel value P_{NORM} in the range [0, 1].

2. If P_{NORM} is in the range [0.3, 0.95], then accept the skin spectra. Otherwise, discard the skin spectra, increment the count of bad skin spectra and recollect the skin spectra at the same arm position.

3. If the total bad skin spectra count reaches five in a single session, reject the entire session.

Reference Ratio Check

The purpose of the reference ratio check is to detect a dirty probe on the monitor. In a session, skin spectra are bounded by two reference spectra denoted by R_1

and R_2, respectively. The reference ratio check is performed as follows:

1. Collect R_1, the skin spectra and then R_2.
2. Compute the average pixel values, R_{1AVG} and R_{2AVG}, respectively.
3. If the ratio $R_{1AVG}/R_{2AVG}<1.003$, accept the session. Otherwise, perform the following:
4. Prompt the user to clean the probe and collect R_2. Discard the original R_2.
5. Compute the average pixel value R_{2AVG}.
6. If the ratio $R_{1AVG}/R_{2AVG}<1.003$, accept the session. Otherwise, reject the entire session.

Standard Deviation Check

The standard deviation check is performed on a set of skin spectra. Let M denote the number of skin spectra in the set. Let S_{ij} denote a particular skin spectra pixel, where i denotes the spectra number {1 ... M} and j denotes the pixel number {1 ... 64}. The standard deviation check is performed as follows:

1. Compute standard deviations of individual pixels: $\sigma_j=STDEV(S_{1j}, S_{2j}, \ldots S_{Mj})$ for j=1 to 64.
2. Compute the average of the 64 standard deviations, denoted as σ_{AVG}.
3. If $\sigma_{AVG}<0.008$, accept the session. Otherwise, reject the session.

Lack-of-Fit (LOF) Test and Optimization

Skin absorbance spectra passes the LOF test if the following is true.

$$F_p<F_c$$

F_c is the critical F statistic for a given level of significance and degrees of freedom

$$F_p = \frac{s_p^2}{s_o^2}$$

s_o^2 mean of calibration spectral residual vector squared norm

s_p^2 squared norm of prediction spectral residual vector

s_o^2 (computed only once)

$$s_o^2 = \frac{\sum_{i=1}^{n} e_i^2}{(n - r - 1)(m - r)}$$

e_i^2 squared norm of spectral residual for calibration vector, i

$$e_i^2 = \tilde{x}_i^T W_{r+1} W_{r+1}^T \tilde{x}_i$$

$\tilde{x}_i$ mean-centered calibration spectra

W the PLS "eigenvectors" in the wavelength domain (from Lanczos bidiagonal decomposition, $X=PBW^T$)

W_{r+1} the last (r+1) to m column vectors of W that span the "noise" subspace

r rank (=25)

m number of channels

n number of spectra in the calibration set

s_p^2 (computed for each prediction spectrum, p)

$$s_p^2 = \frac{e_p^2}{(m - r)}$$

e_p^2 squared norm of spectral residual for prediction vector, p

$$e_p^2 = \tilde{x}_p^T W_{r+1} W_{r+1}^T \tilde{x}_p$$

$\tilde{x}_p$ prediction spectrum mean-centered to calibration set

For example, if r=25; m=43; and n=200, F_c=1.58 at 0.05 level of significance. Therefore, if F_p<1.58, the prediction spectrum p passes the LOF test.

LOF threshold, T=(1-level of significance). Optimize LOF threshold as follows:

During weeks seven and eight of calibration, develop LOF threshold by the following procedure:

Using the first six weeks of data and self-prediction, perform LOF threshold optimization. If a threshold T can be found such that SEC<30 mg/dL and % Prediction>80%, use this value of T (else, T=1.0). Using

data from weeks seven and eight, using threshold = T, confirm that SEP<30mg/dL and % Prediction>80%. If not, set T=1.0.

PLS Decomposition

1. Transform the Matrix X_{avg}

The purpose of PLS decomposition is to produce regression coefficients from the mean-centered absorbance spectra and invasive readings provided. Use the bidiagonalization algorithm described below to transform the matrix X_{avg} to rank p into three matrices, UBV^T, using Y_{avg}.

p	rank used
m	number of channels used +1 for the interpolated glucose value (number of columns)
n	number of spectra (number of rows)
X	an n by m matrix
X_{avg}	a matrix that contains mean-centered spectral data from the X matrix
Y_{avg}	a vector containing mean-centered glucose values
rank p	the number of factors actually used in the bidiagonalization function
U	an n by p orthogonal matrix whose columns contain PLS scores, projections into n dimensional space that are themselves derived from the spectra and glucose (X and Y matrices, respectively). The PLS scores show normalcy and outliers in spectra.
B	a p by p diagonal-superdiagonal matrix having nonzero elements on the diagonal and the superdiagonal; the elements demonstrate the magnitude of the PLS scores
V	a p by m orthonormal matrix whose columns are the basis vectors of the column space of X_{avg} and whose rows are the loadings, which demonstrate the importance of each column of X_{avg}.

2. The Algorithm for Bidiagonalization

The bidiagonalization algorithm uses the Y_{avg} vector to transform the matrix X_{avg} for each rank up to p

rank into three matrices, UBV^T. This algorithm is presented below. The lower case letters represent a column of a matrix. The subscript represents the particular element. Some basic terms:

u_j j^{th} PLS scores or j^{th} column of U
v_j j^{th} column of V
q_j pre-normalized v_j
p_j pre-normalized u_j
α_j j^{th} diagonal of B
β_j j^{th} superdiagonal of B

The steps of the algorithm follow.

1a. Mean center to get X_{avg} and Y_{avg}
1b. Compute the starting vector, $q_1=X_{avg}{}^TY_{avg}$ (use to maximize correlation)
1c. Compute $v_1=q_1/\|q_1\|$
1d. Compute $p_1=X_{avg}v_1$

Then, for each rank, 1 through p, compute the following.

2. Compute $u_j=p_j/\|p_j\|$
3. Column j of V=v_j. Column j of U=u_j. (builds one column of each matrix, V and U, for each rank)
4. $\alpha_j=j^{th}$ diagonal of B=norm of p_j (builds one diagonal of matrix B for each rank)
5. $q_{j+1}=u_j{}^TX_{avg} - \alpha_j v_j$

Perform modified Gram-Schmidt algorithm to insure v_j is orthogonal to the other columns of V.

6. $\beta_j=j^{th}$ superdiagonal of B=norm of q_{j+1}
7. Compute $v_{j+1}=q_{j+1}/\|q_{j+1}\|$
8. $p_{j+1}=X_{avg}v_{j+1} - \beta_j u_j$
9. Let j=j+1 and go to Step 2.

Stop this procedure when either the norm of q=0 or when j is greater than rank p.

$X_{avg}=UBV^T$

$X_{avg}V=UBV^TV$ since we are using an orthonormal basis, $V^TV=I_p$, so

$X_{avg}V=UB$ (6)

By fundamental linear algebra, Ae_i=the i^{th} column of any matrix A and e_i^TA=the i^{th} row of A, where e is the elementary matrix. This can be applied since it has been established that B is a diagonal-superdiagonal matrix. Therefore,

$Be_i=\beta_{I-1}e_{i-1} + \alpha_I e_i$ for i>1, and (7)

$e_i^TB=\alpha_I e_i^T + \beta_i e_{i+1}$ for i<n (8)

Using equations 7 and 8 to substitute in the decomposition, equations for α_i and β_i can be obtained. The following is the derivation of equations for α_j and β_j, which give the equations for p_{j+1} and q_{j+1}:

$\underline{\alpha_j}$	$\underline{\beta_j}$
$X_{avg}V=UB$	$U^TX_{avg}=BV^T$
$X_{avg}Ve_i=UBe_i$	$X_{avg}^TU=VB^T$
$X_{avg}Ve_i=U(\beta_{i-1}e_{i-1} + \alpha_i e_i)$	$X_{avg}^TUe_i=VB^Te_i$
$X_{avg}V=U\beta_{i-1}e_{i-1} + U\alpha_i e_i$	$X_{avg}^TU=V(\alpha_i e_i^T + \beta_i e_{i+1})$
$U\alpha_i e_i=X_{avg}V - U\beta_{i-1}e_{i-1}$	$X_{avg}^TU=V\alpha_i e_i^T + V\beta_i e_{i+1}$
$P_{j+1}=X_{avg}V - U\beta_{i-1}e_{i-1}$ (9)	$V\beta_i e_{i+1}=X_{avg}^TU - V\alpha_i e_i^T$
	$q_{j+1}=X_{avg}^TU - V\alpha_i e_i^T$ (10)

Randomized Bin-Averaging (RBA) Calibration Method

Start with approximately 120 sittings x 6 sessions x 4 subsessions=2,880 absorbance spectra available for calibration. Randomly pick three out of 2,880 spectra. Make sure not to include the same spectrum twice. Form a "linear combo spectrum" by adding the three up going "+ + -" on both their absorbance and their invasive readings. Replace the three picked spectra back into the population of 2,880. Sort the invasive readings of the linear combo spectrum into one of ten different glucose bins: first bin is from 0-40 mg/dL, the second is from 40-80 mg/dL, ..., tenth bin is from 360-400 mg/dL. Discard those linear combo spectra which have invasive readings of <0 mg/dL or >400 mg/dL. Repeat until each glucose bin contains at least 30 x 90 = 2,700 linear combo spectra. Within each glucose bin, form thirty averages over ninety (ntavg=90) linear combo spectra. These averages constitute the population of 10 bins x 30 averages = 300 calibration

spectra. Perform PLS (rank=25) using the 300 calibration spectra and obtain the calibration vector. Use this calibration vector for obtaining monitor measurements in the period succeeding the calibration period.

Slope and Intercept Correction (SIC) Calibration Method

1. Perform PLS (rank=25) using the 2,880 spectra (approx.) available and obtain the calibration vector.

2. Perform "self-prediction" whereby the calibration spectra are used to obtain $monitor_c$ measurements which are regressed against the corresponding invasive reading values (HQ_c).

$$Monitor_c = k_1 * (HQ_c) + k_0$$

3. Use the calibration vector from step 1 for obtaining monitor measurements in the period succeeding the calibration period and apply the following correction using k_0, the calibration intercept and k_1, the calibration slope. The corrected prediction

$$Monitor^{SIC} = (Monitor - k_0)\frac{1}{k_1}$$

Procedure for Selection between SIC and RBA Calibration Methods for Each Patient

Split 60-day calibration data into Set 1 (six week approx.) for calibration and Set 2 (two weeks approx.) for testing. Select the method which performs better on the following tests (in descending order of importance) using Set 2 predictions:

1. hypothesis tests of equality of slope to 1 and intercept to 0
2. closeness of slope to 1
3. smallness of SEP

Quality Monitoring Cutoff Value

The purpose of the quality monitoring cutoff value is to provide the patient with a threshold under which the difference between the monitor measurement and invasive reading value has to lie for quality control purposes. For paired monitor measurement (x_i) and invasive

value (y_i) for data collected during calibration define a root mean square (RMS) error as follows:

$$RMS = \sqrt{\frac{1}{M}\sum_{i=1}^{M}(y_i - x_i)^2}$$

where M is the number of paired results

QM cutoff value=2•RMS

Control Standard Check

The purpose of the control standard check is to identify any gross malfunction of the monitor due to conditions, such as dirty probe, lamp outage, etc. The following steps are performed for the control standard check.

1. Collect risk analysis hazard data for a patient's device or transfer prototypical hazard data from monitor risk analysis testing.

2. Collect calibration data from population of N subjects. Calibration data shall consist of spectral readings of patient skin and control standard material and reference blood glucose monitoring device. The control standard material shall have a stated target concentration and the target concentration from each lot of control material shall be provided by manufacturing.

3. Use analysis of variance (ANOVA) to determine control limits. If as many as four patients will use a single device at several sites, then use the nested analysis of variance as follows:

$$R_{ij} = \tau_i + \beta_i + \epsilon_{ij}$$

where τ is site and β is patient within site. The "Root MSE" from ANOVA modeling allows us an estimate of the control limits to be applied to future patients.

4. Determine the control limit as:

$$(CL) = 3(\text{Root MSE})$$

5. Determine upper control limit as:

Upper = Target Glucose Concentration + CL

6. Determine lower control limit as:

Lower = Target Glucose Concentration - CL

7. Append to the patient's calibration data all control readings during the calibration period.

8. Determine control material calibration vector from appended data.

9. Apply control material calibration vector to both the control readings and patient skin readings during the calibration period.

10. Apply control material calibration vector to risk and hazard data.

11. Select the calibration vector rank by optimizing the performance of the calibration vector. Optimal performance is such that we maximize the control material readings falling within the control limits during calibration and also maximize the number of control material readings falling out when testing hazard data.

Thus, as will be understood by one of ordinary skill in the art, the present invention provides a method of calibrating a noninvasive glucose monitor for an individual patient which overcomes the problems associated with previously known calibration methods. The disclosed method provides a personalized calibration method that spans a patient's skin, the time between readings and the glucose variation inherent in a diabetic condition.

It will be readily appreciated by those skilled in the art that modifications may be made to the invention without departing from the concepts disclosed in the foregoing description. Such modifications are to be considered as included within the following claims unless the claims, by their language, expressly state otherwise. Accordingly, the particular embodiments described in detail herein are illustrative only and are not limiting to the scope of the invention which is to be given the full breadth of the appended claims and any and all equivalents thereof.

WE CLAIM:

1. A method of calibrating a noninvasive glucose monitor for prospective noninvasive glucose determination, comprising the steps of:

measuring spectroscopic transflectance readings of a patient's skin using a noninvasive glucose monitor;

measuring the patient's blood glucose level with an invasive glucose monitor; and

correlating the noninvasive and invasive measurements to form an individual algorithm for each patient.

2. The method as claimed in claim 1, including spatially adjusting a position of the patient's skin with respect to a probe of the noninvasive glucose monitor while collecting transflectance measurements such that multiple readings are taken on the patient's skin.

3. The method as claimed in claim 1, including taking measurements over at least a two-epoch period.

4. The method as claimed in claim 1, including taking measurements over a plurality of glucose levels in the patient.

5. The method as claimed in claim 1, including converting the spectroscopic transflectance readings to glucose levels using the individual algorithm.

6. The method as claimed in claim 1, including replicating the transflectance measurements until there is no improvement in sampling variance.

7. The method as claimed in claim 2, including spatially adjusting the position of the patient's skin or the probe by a plurality of dithering movements.

8. The method as claimed in claim 2, including taking multiple transflectance measurements in a pattern on the patient's skin.

9. The method as claimed in claim 3, including using the measurements from the first epoch to calibrate the noninvasive monitor.

10. The method as claimed in claim 3, including using the readings from the second epoch to determine the patient's glucose level.

11. The method as claimed in claim 3, wherein the number of transflectance readings is determined by the formula $N \geq Z\sigma/L$, where N is the number of readings during calibration, Z is approximated by the standard normal statistic, σ represents the patient's skin variation and L relates to a desired clinical accuracy of the patient's skin variation.

12. The method as claimed in claim 3, including adjusting the number of transflectance measurements over time after determining a between-day variation.

13. The method as claimed in claim 5, wherein the first epoch lasts for a period of about 2-60 days.

14. The method as claimed in claim 12, including determining the between-day variation by calculating the mean and standard deviation of spectra over about two to seven days.

15. The method as claimed in claim 1, wherein the transflectance redings of the patient's skin are taken by illuminating an area of the patient's skin and taking multiple transflectance readings over this area.

16. A method of calibrating a noninvasive glucose monitor for prospective noninvasive glucose determination, comprising the steps of:

measuring spectroscopic transflectance readings of a patient's skin using a noninvasive glucose monitor;

measuring the patient's blood glucose level with an invasive glucose monitor;

correlating the noninvasive and invasive measurements to form an individual algorithm for each patient;

spatially adjusting a position of the patient's skin with respect to a probe of the noninvasive glucose monitor while collecting transflectance measurements such that multiple readings are taken on the patient's skin;

taking measurements over at least a two-epoch period;

taking measurements over a plurality of glucose levels in the patient; and

converting the spectroscopic transflectance readings to glucose levels using the individual algorithm.

17. The method as claimed in claim 16, including spatially adjusting the position of the patient's skin or the probe by a plurality of dithering movements.

18. The method as claimed in claim 16, including taking multiple transflectance measurements in a pattern on the patient's skin.

19. The method as claimed in claim 16, including using the measurements from the first epoch to calibrate the noninvasive monitor.

20. The method as claimed in claim 16, including using the readings from the second epoch to determine the patient's glucose level.

21. A method of calibrating a noninvasive glucose monitor for prospective noninvasive glucose determination, comprising the steps of:

measuring spectroscopic transflectance readings of a patient's skin using a noninvasive glucose monitor;

measuring the patient's blood glucose level with an invasive glucose monitor;

correlating the noninvasive and invasive measurements to form an individual algorithm for each patient;

spatially adjusting a position of the patient's skin with respect to a probe of the noninvasive glucose monitor while collecting transflectance measurements such that multiple readings are taken on the patient's skin;

taking measurements over at least a two-epoch period;

taking measurements over a plurality of glucose levels in the patient;

converting the spectroscopic transflectance readings to glucose levels using the individual algorithm;

spatially adjusting the position of the patient's skin or the probe by a plurality of dithering movements;

taking multiple transflectance measurements in a pattern on the patient's skin;

using the measurements from the first epoch to calibrate the noninvasive monitor; and

using the readings from the second epoch to determine the patient's glucose level.

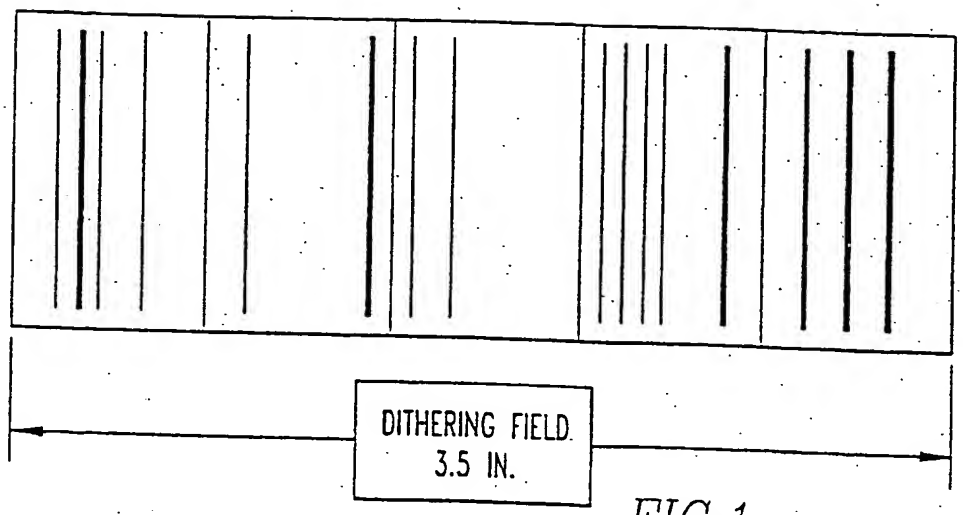
DITHERING FIELD
3.5 IN.

FIG.1

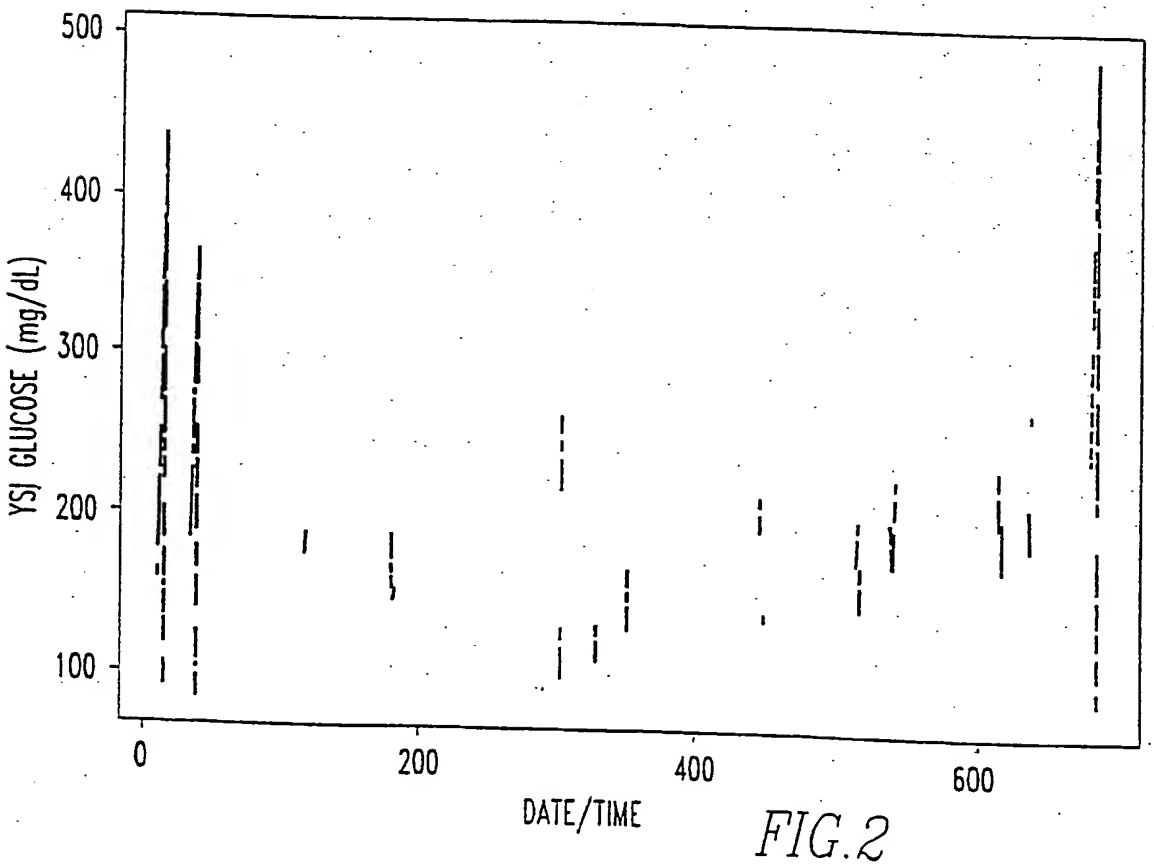
500
400
300
200
100
YSI GLUCOSE (mg/dL)
0
200
400
600
DATE/TIME

FIG.2

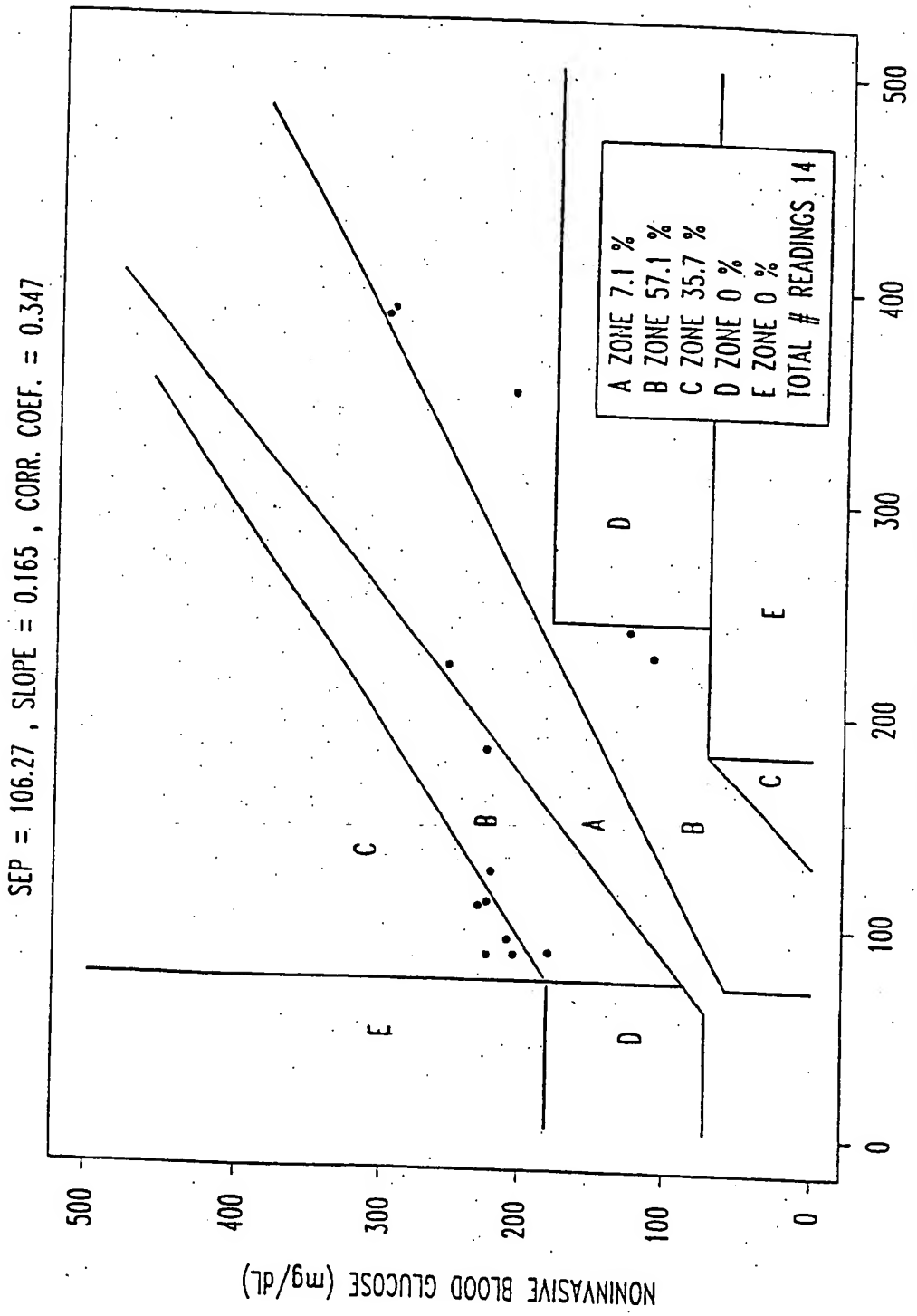
SEP = 106.27 , SLOPE = 0.165 , CORR. COEF. = 0.347
NONINVASIVE BLOOD GLUCOSE (mg/dL)
YSI REFERENCE BLOOD GLUCOSE (mg/dL)
A ZONE 7.1 %
B ZONE 57.1 %
C ZONE 35.7 %
D ZONE 0 %
E ZONE 0 %
TOTAL # READINGS 14
0
100
200
300
400
500
A
B
C
D
E

FIG. 3

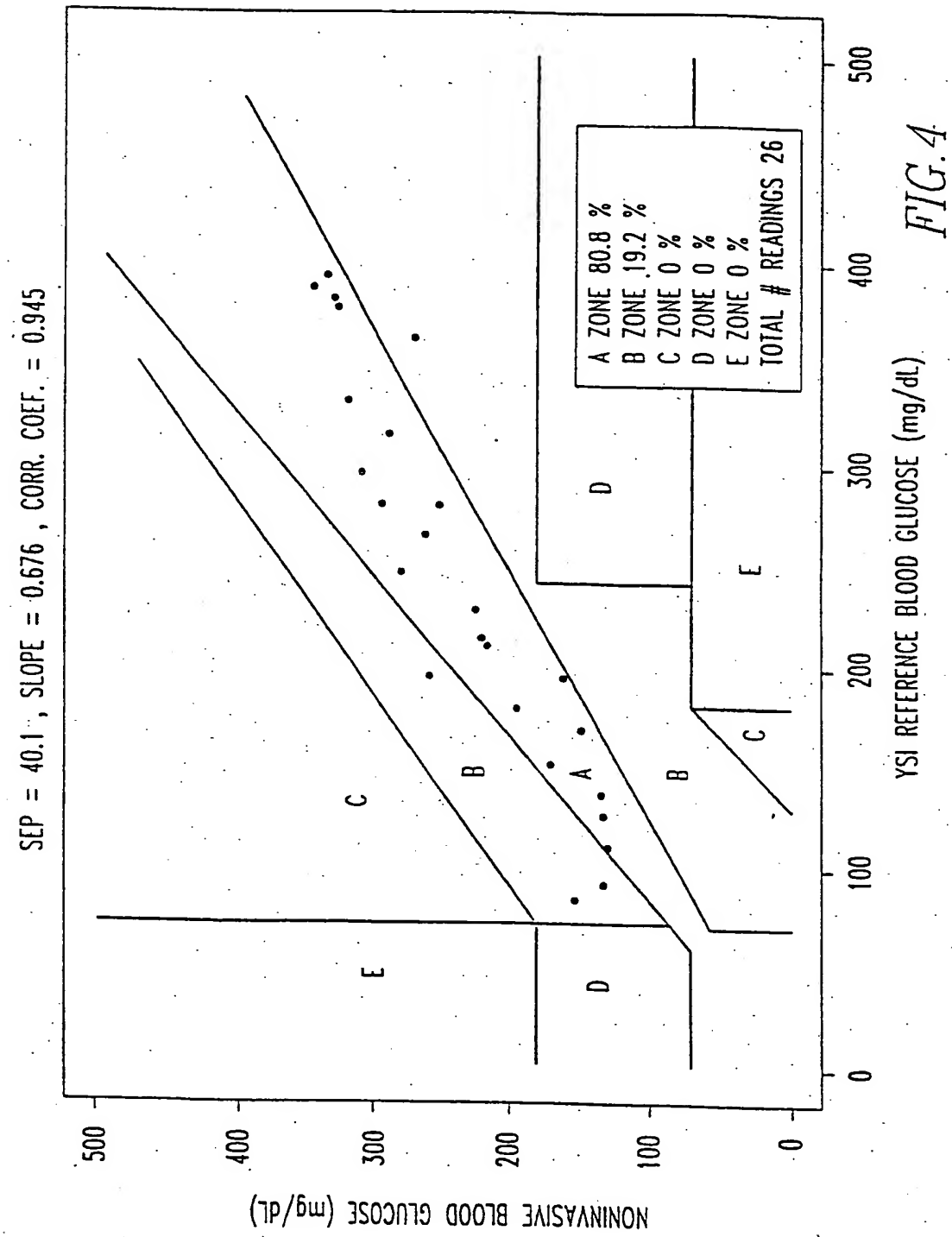
SEP = 40.1 , SLOPE = 0.676 , CORR. COEF. = 0.945
NONINVASIVE BLOOD GLUCOSE (mg/dL)
YSI REFERENCE BLOOD GLUCOSE (mg/dL)
A ZONE 80.8 %
B ZONE 19.2 %
C ZONE 0 %
D ZONE 0 %
E ZONE 0 %
TOTAL # READINGS 26
0
100
200
300
400
500
A
B
C
D
E

FIG. 4

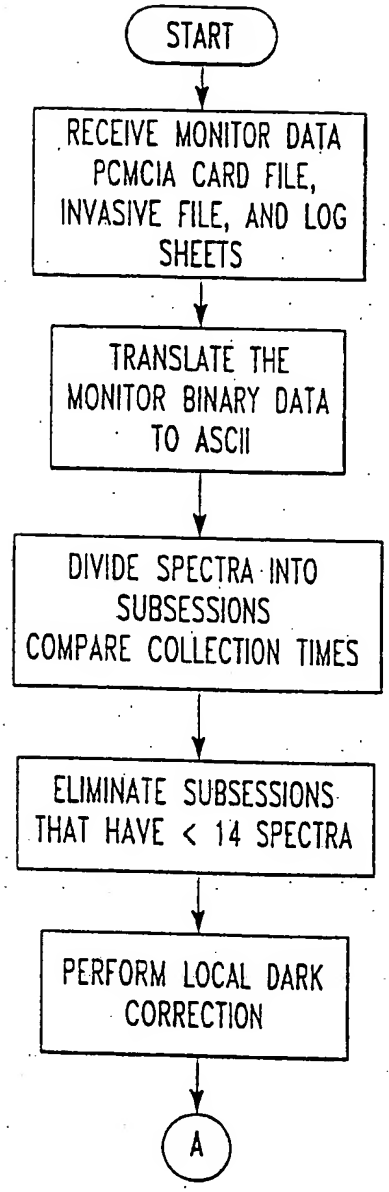

FIG.5A1

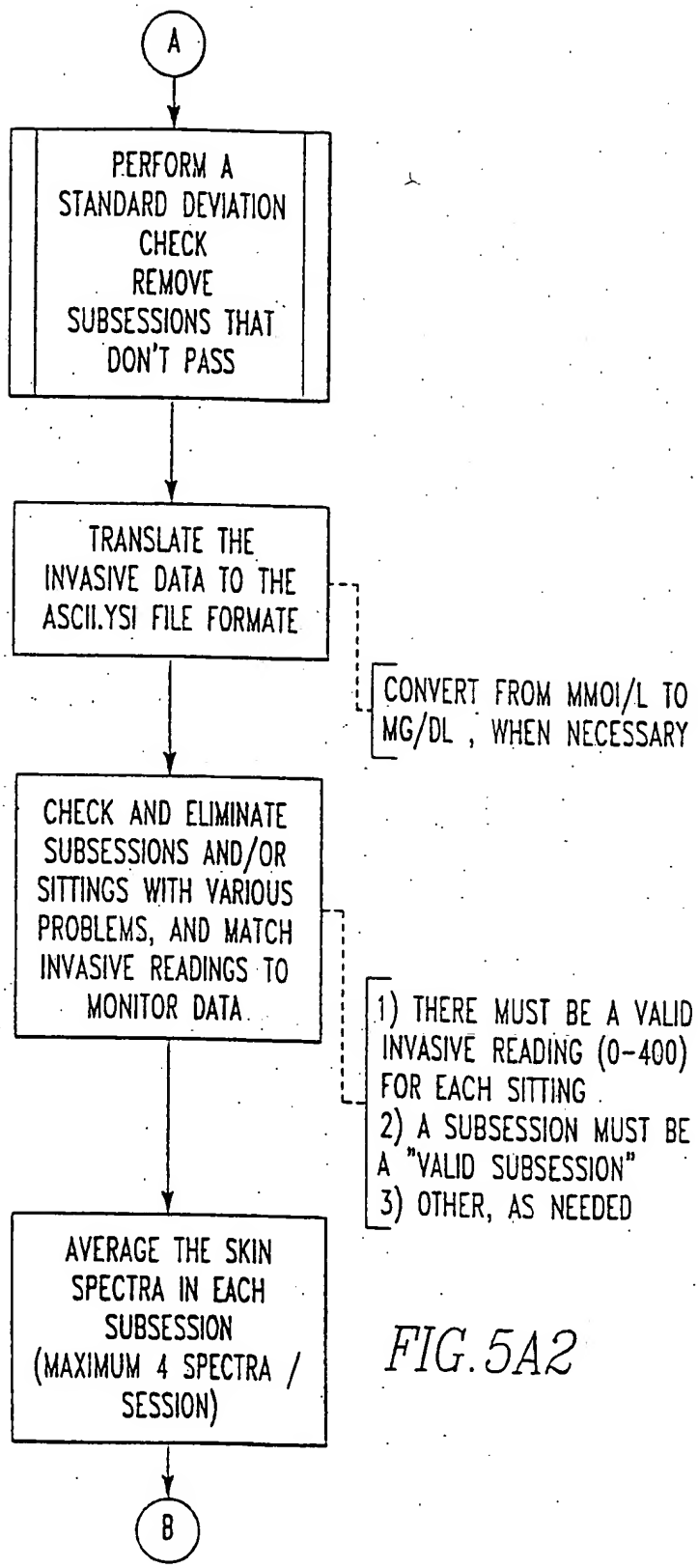

FIG.5A2

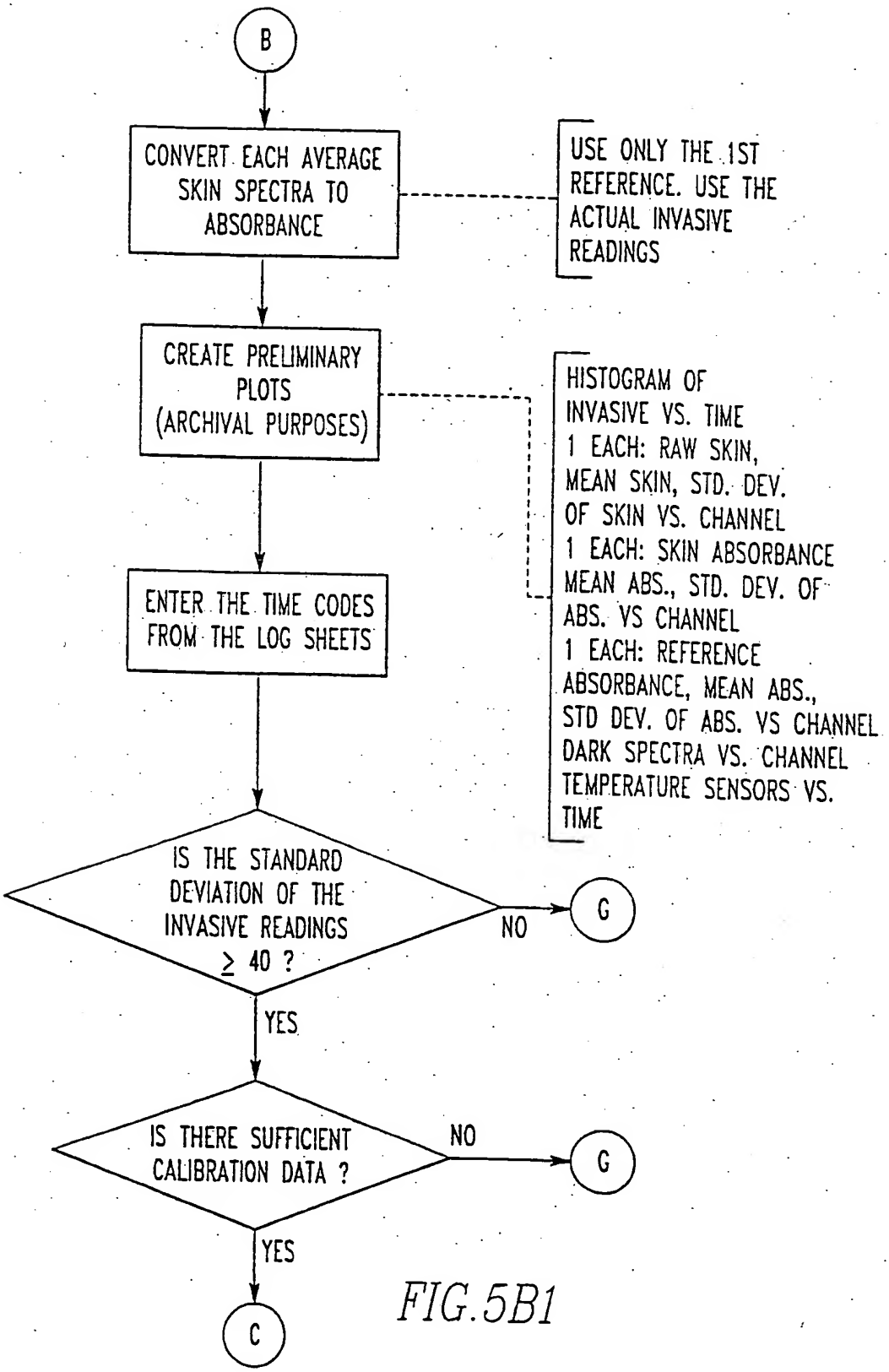
B
CONVERT EACH AVERAGE SKIN SPECTRA TO ABSORBANCE
USE ONLY THE 1ST REFERENCE. USE THE ACTUAL INVASIVE READINGS
CREATE PRELIMINARY PLOTS (ARCHIVAL PURPOSES)
HISTOGRAM OF INVASIVE VS. TIME
1 EACH: RAW SKIN, MEAN SKIN, STD. DEV. OF SKIN VS. CHANNEL
1 EACH: SKIN ABSORBANCE MEAN ABS., STD. DEV. OF ABS. VS CHANNEL
1 EACH: REFERENCE ABSORBANCE, MEAN ABS., STD DEV. OF ABS. VS CHANNEL
DARK SPECTRA VS. CHANNEL
TEMPERATURE SENSORS VS. TIME
ENTER THE TIME CODES FROM THE LOG SHEETS
IS THE STANDARD DEVIATION OF THE INVASIVE READINGS ≥ 40 ?
NO
G
YES
IS THERE SUFFICIENT CALIBRATION DATA ?
NO
G
YES
C

FIG.5B1

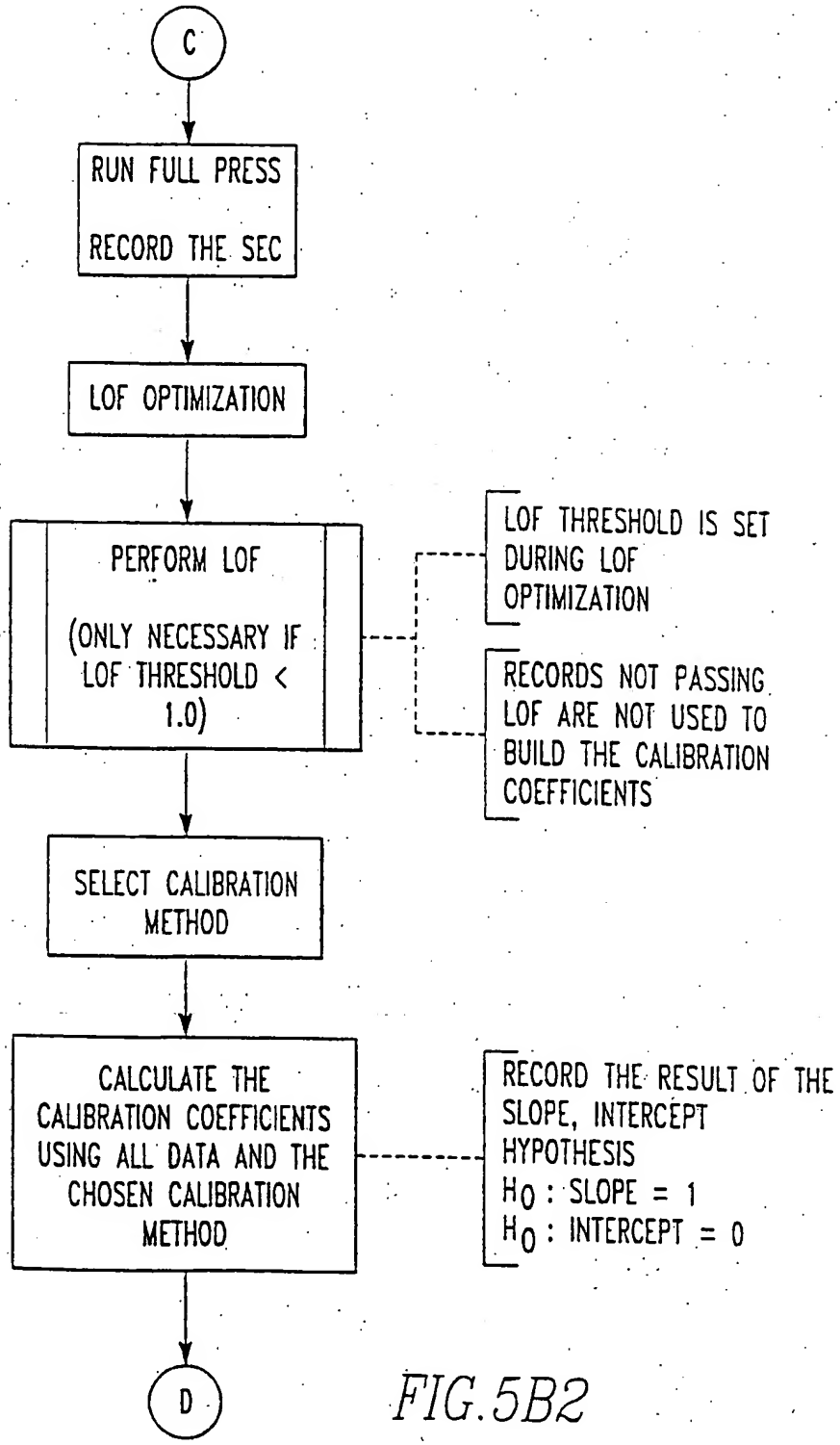
C
RUN FULL PRESS
RECORD THE SEC
LOF OPTIMIZATION
PERFORM LOF
(ONLY NECESSARY IF LOF THRESHOLD < 1.0)
LOF THRESHOLD IS SET DURING LOF OPTIMIZATION
RECORDS NOT PASSING LOF ARE NOT USED TO BUILD THE CALIBRATION COEFFICIENTS
SELECT CALIBRATION METHOD
CALCULATE THE CALIBRATION COEFFICIENTS USING ALL DATA AND THE CHOSEN CALIBRATION METHOD
RECORD THE RESULT OF THE SLOPE, INTERCEPT HYPOTHESIS
H_0 : SLOPE = 1
H_0 : INTERCEPT = 0
D

FIG.5B2

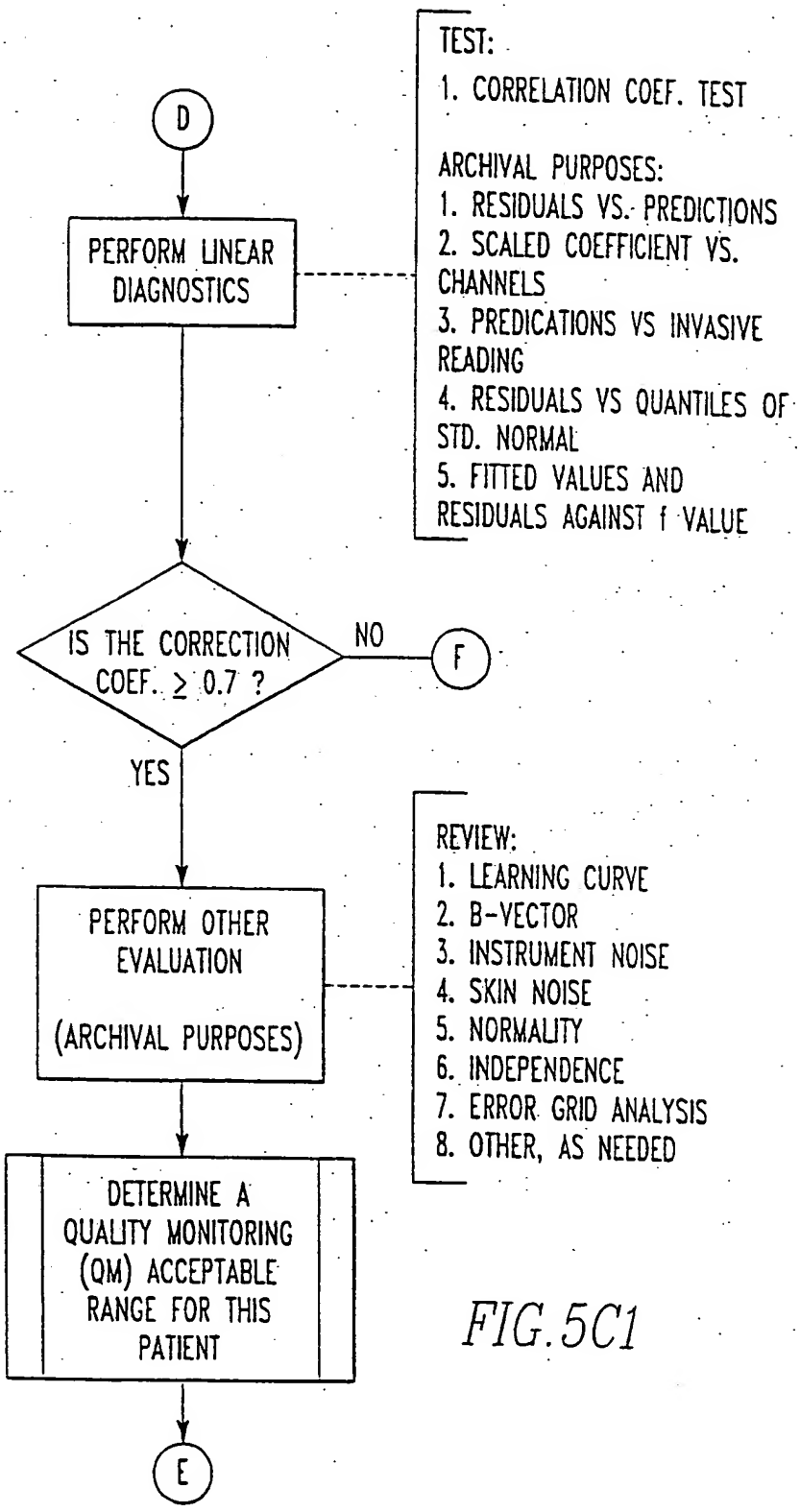
D
PERFORM LINEAR DIAGNOSTICS
TEST:
1. CORRELATION COEF. TEST
ARCHIVAL PURPOSES:
1. RESIDUALS VS. PREDICTIONS
2. SCALED COEFFICIENT VS. CHANNELS
3. PREDICATIONS VS INVASIVE READING
4. RESIDUALS VS QUANTILES OF STD. NORMAL
5. FITTED VALUES AND RESIDUALS AGAINST f VALUE
IS THE CORRECTION COEF. ≥ 0.7 ?
NO
F
YES
PERFORM OTHER EVALUATION
(ARCHIVAL PURPOSES)
REVIEW:
1. LEARNING CURVE
2. B-VECTOR
3. INSTRUMENT NOISE
4. SKIN NOISE
5. NORMALITY
6. INDEPENDENCE
7. ERROR GRID ANALYSIS
8. OTHER, AS NEEDED
DETERMINE A QUALITY MONITORING (QM) ACCEPTABLE RANGE FOR THIS PATIENT
E

FIG.5C1

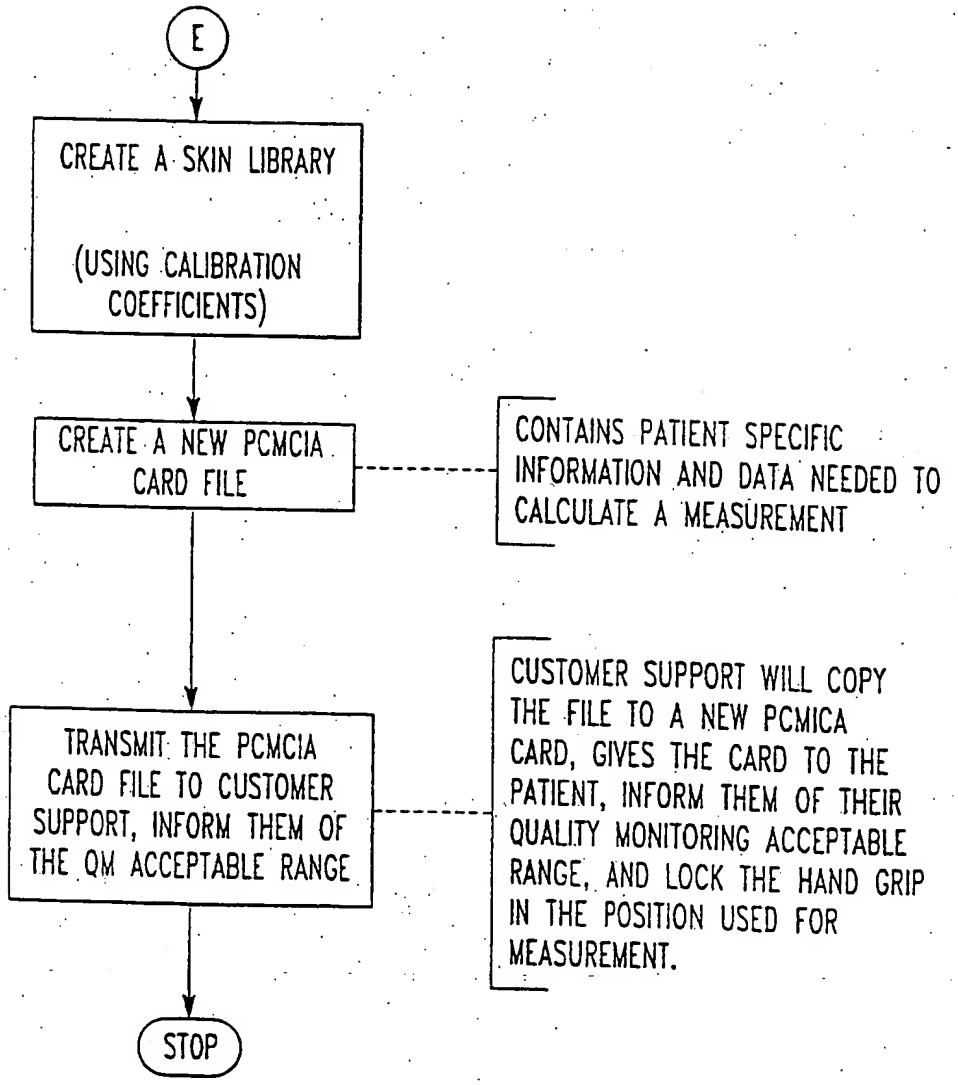
E
CREATE A SKIN LIBRARY
(USING CALIBRATION COEFFICIENTS)
CREATE A NEW PCMCIA CARD FILE
CONTAINS PATIENT SPECIFIC INFORMATION AND DATA NEEDED TO CALCULATE A MEASUREMENT
TRANSMIT THE PCMCIA CARD FILE TO CUSTOMER SUPPORT, INFORM THEM OF THE QM ACCEPTABLE RANGE
CUSTOMER SUPPORT WILL COPY THE FILE TO A NEW PCMICA CARD, GIVES THE CARD TO THE PATIENT, INFORM THEM OF THEIR QUALITY MONITORING ACCEPTABLE RANGE, AND LOCK THE HAND GRIP IN THE POSITION USED FOR MEASUREMENT.
STOP

FIG.5C2

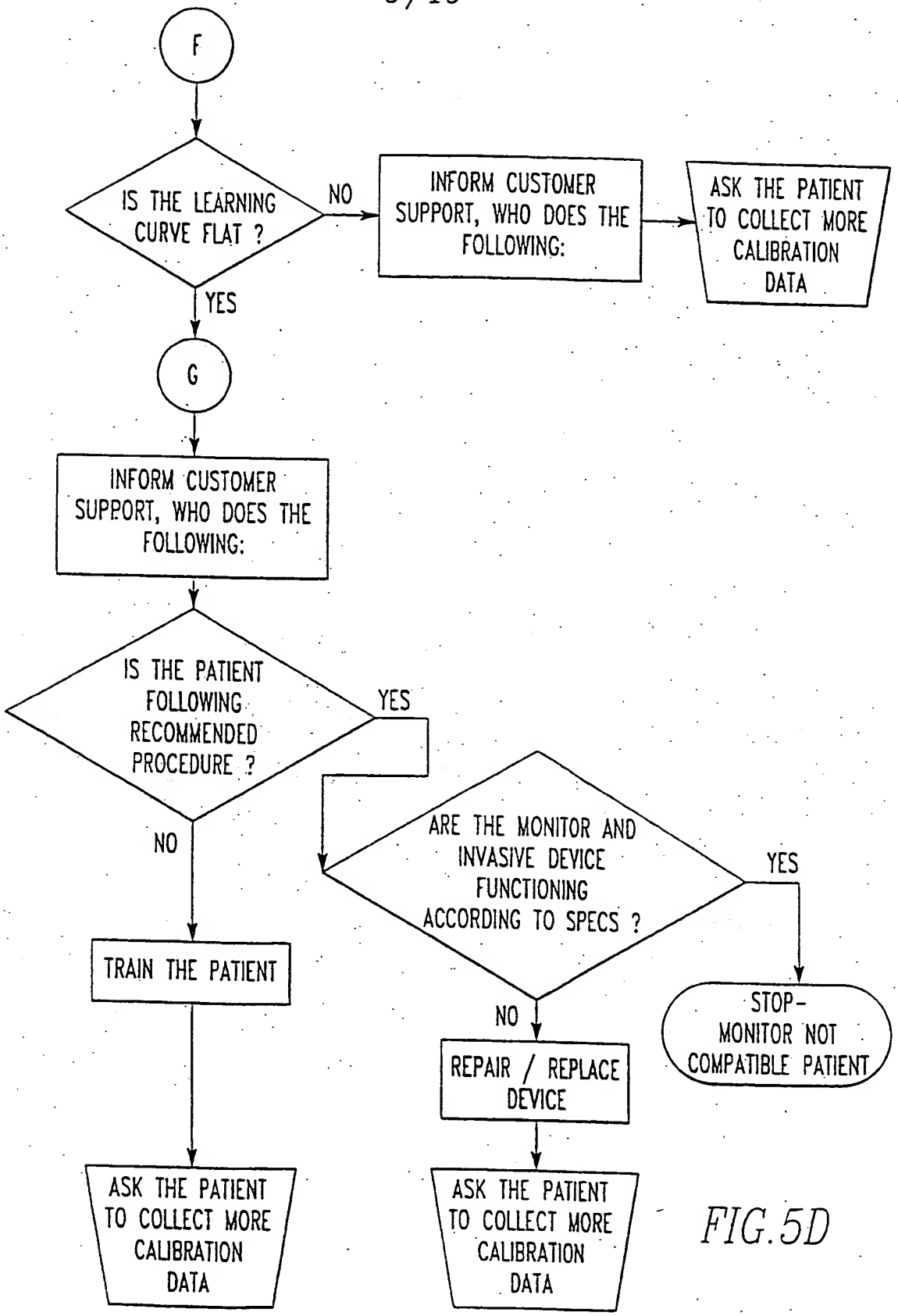
F
IS THE LEARNING CURVE FLAT ?
NO
INFORM CUSTOMER SUPPORT, WHO DOES THE FOLLOWING:
ASK THE PATIENT TO COLLECT MORE CALIBRATION DATA
YES
G
INFORM CUSTOMER SUPPORT, WHO DOES THE FOLLOWING:
IS THE PATIENT FOLLOWING RECOMMENDED PROCEDURE ?
YES
NO
TRAIN THE PATIENT
ASK THE PATIENT TO COLLECT MORE CALIBRATION DATA
ARE THE MONITOR AND INVASIVE DEVICE FUNCTIONING ACCORDING TO SPECS ?
YES
NO
STOP- MONITOR NOT COMPATIBLE PATIENT
REPAIR / REPLACE DEVICE
ASK THE PATIENT TO COLLECT MORE CALIBRATION DATA

FIG.5D

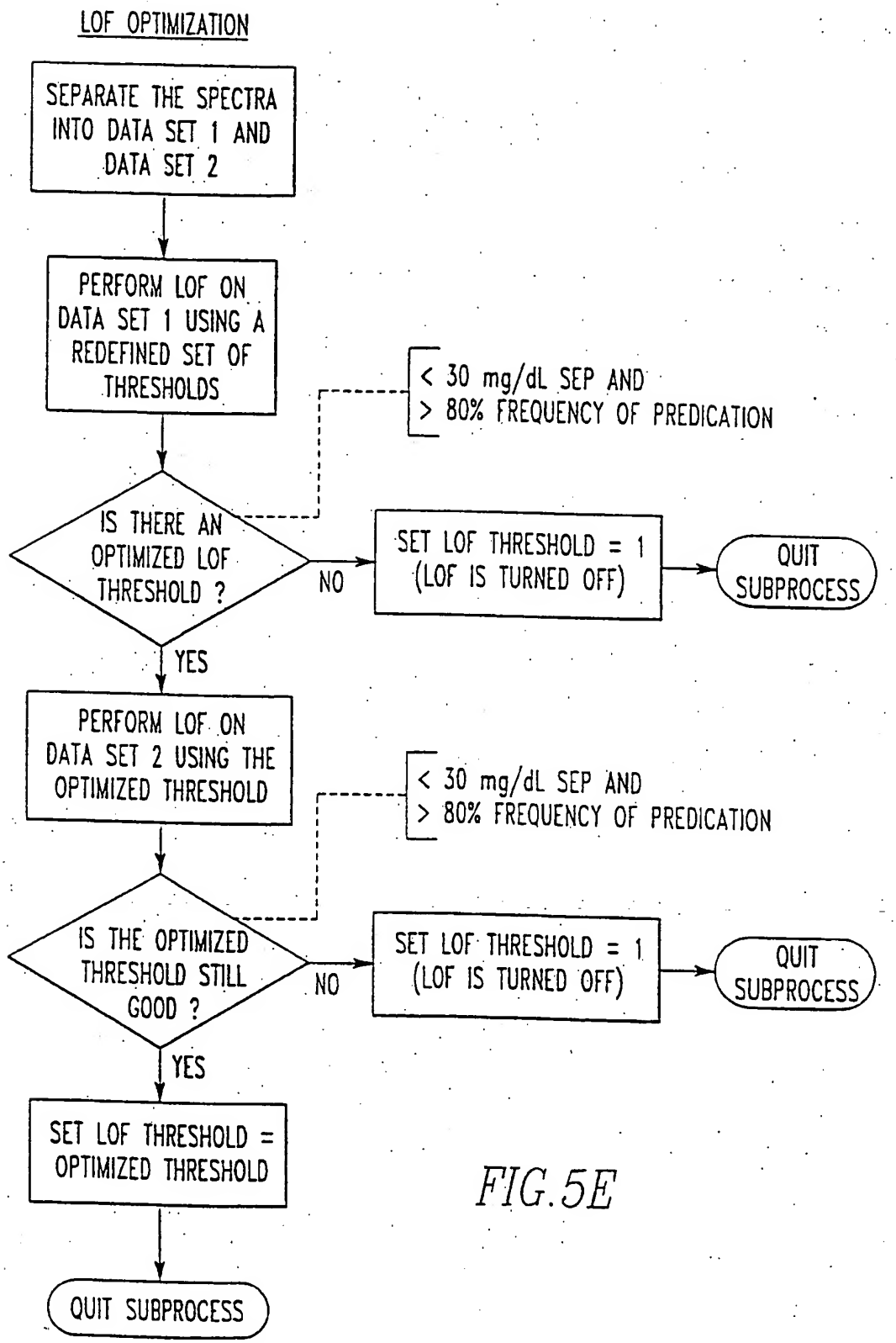
LOF OPTIMIZATION
SEPARATE THE SPECTRA INTO DATA SET 1 AND DATA SET 2
PERFORM LOF ON DATA SET 1 USING A REDEFINED SET OF THRESHOLDS
< 30 mg/dL SEP AND
> 80% FREQUENCY OF PREDICATION
IS THERE AN OPTIMIZED LOF THRESHOLD ?
NO
SET LOF THRESHOLD = 1 (LOF IS TURNED OFF)
QUIT SUBPROCESS
YES
PERFORM LOF ON DATA SET 2 USING THE OPTIMIZED THRESHOLD
< 30 mg/dL SEP AND
> 80% FREQUENCY OF PREDICATION
IS THE OPTIMIZED THRESHOLD STILL GOOD ?
NO
SET LOF THRESHOLD = 1 (LOF IS TURNED OFF)
QUIT SUBPROCESS
YES
SET LOF THRESHOLD = OPTIMIZED THRESHOLD
QUIT SUBPROCESS

FIG.5E

SELECT CALIBRATION METHOD-DETAILS 11/19

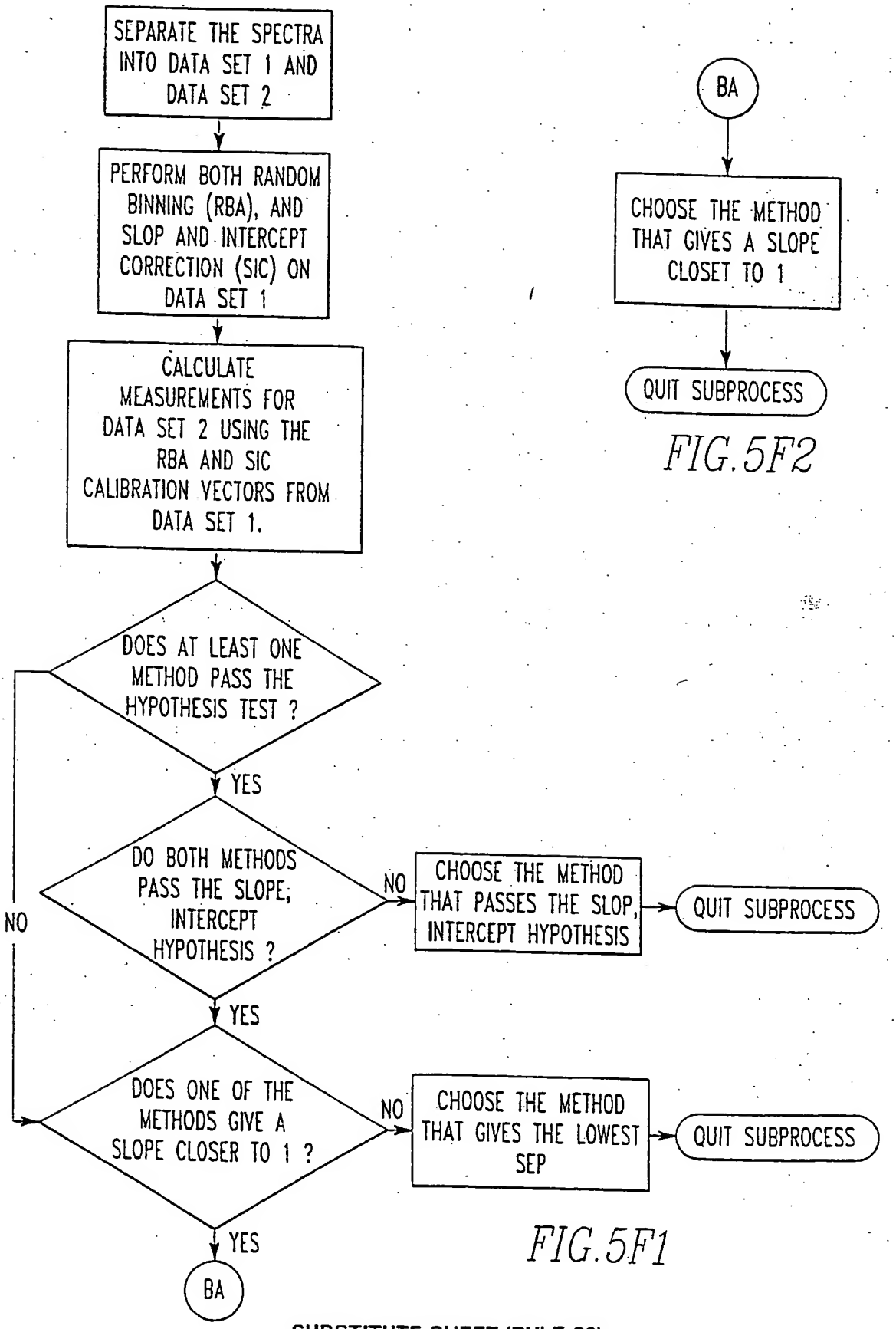

FIG.5F1

FIG.5F2

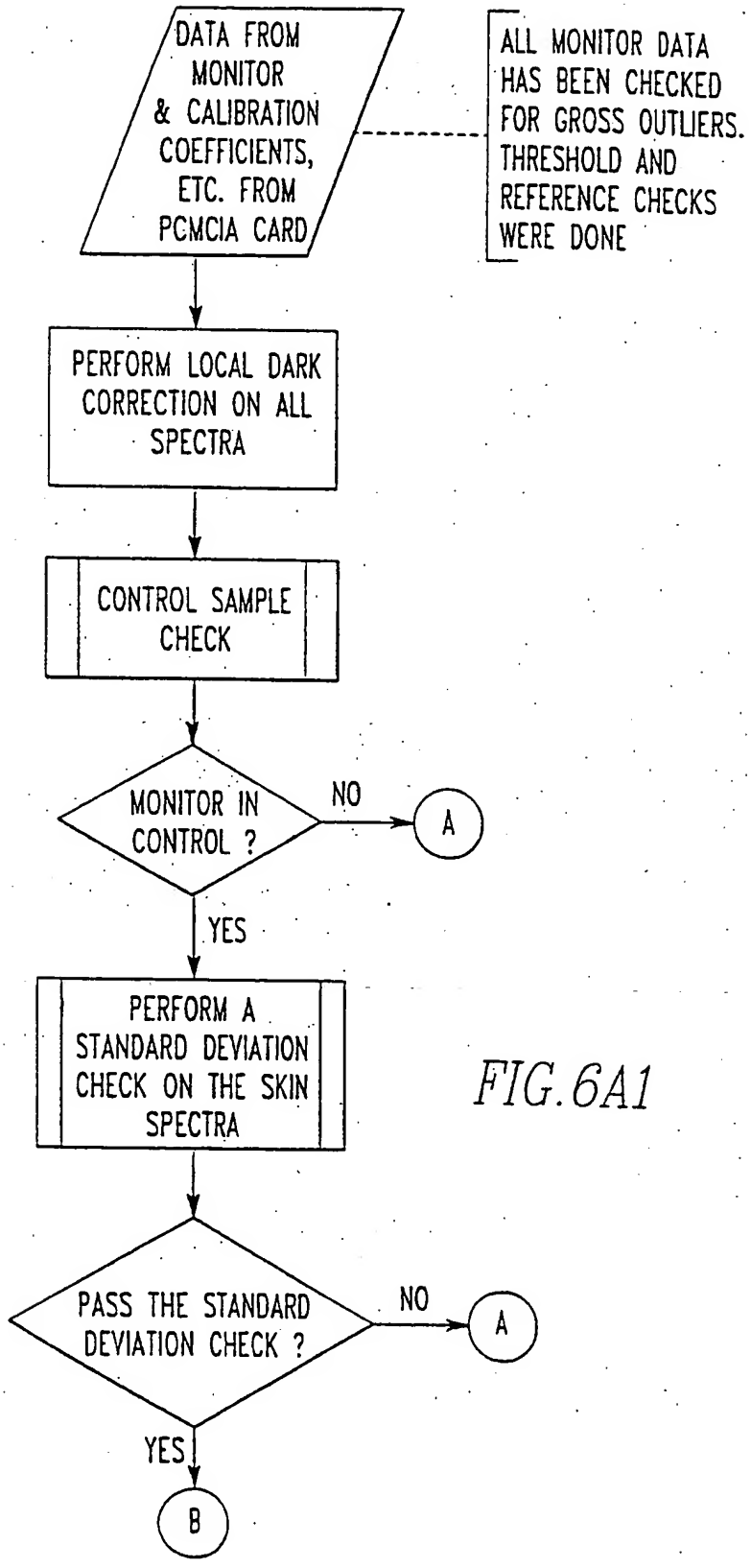
DATA FROM MONITOR & CALIBRATION COEFFICIENTS, ETC. FROM PCMCIA CARD
ALL MONITOR DATA HAS BEEN CHECKED FOR GROSS OUTLIERS. THRESHOLD AND REFERENCE CHECKS WERE DONE
PERFORM LOCAL DARK CORRECTION ON ALL SPECTRA
CONTROL SAMPLE CHECK
MONITOR IN CONTROL ?
NO
A
YES
PERFORM A STANDARD DEVIATION CHECK ON THE SKIN SPECTRA
PASS THE STANDARD DEVIATION CHECK ?
NO
A
YES
B

FIG. 6A1

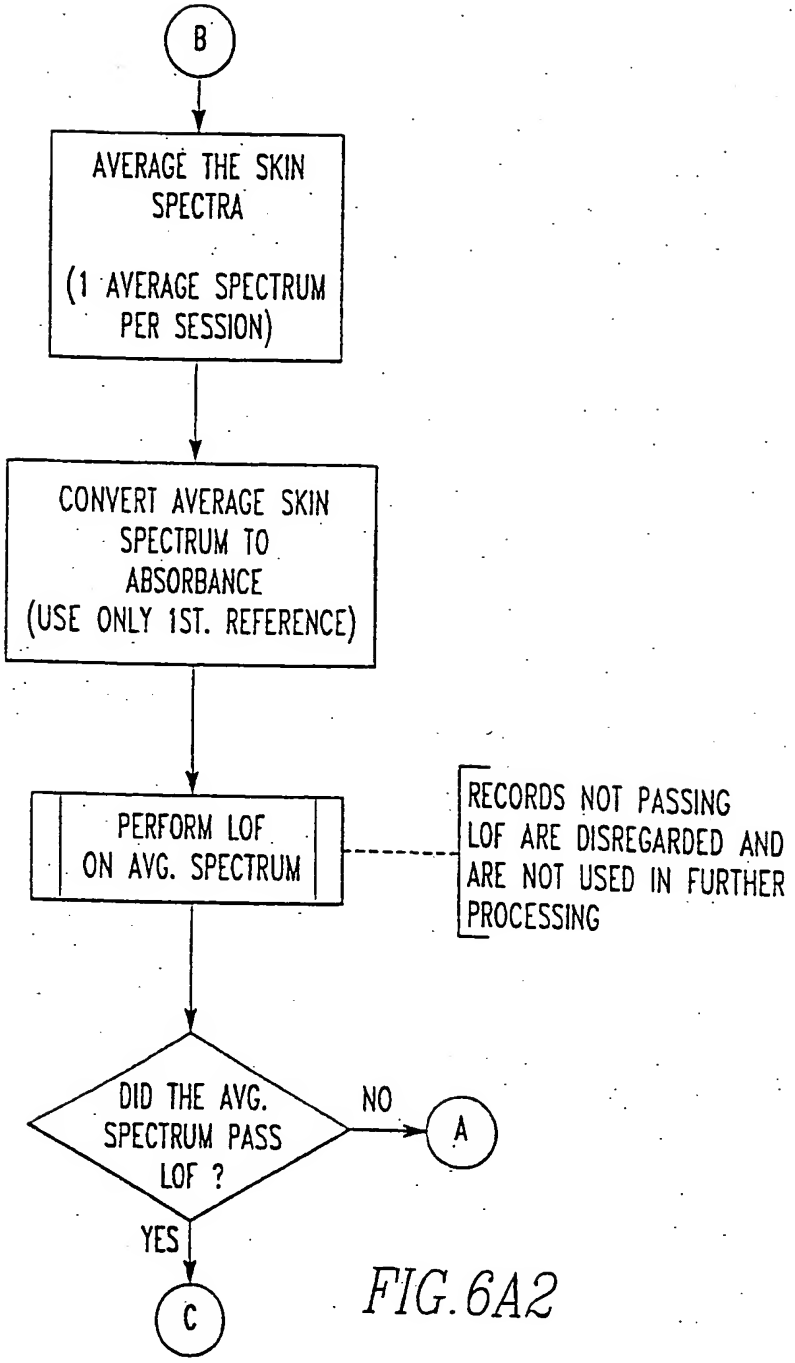
B
AVERAGE THE SKIN SPECTRA
(1 AVERAGE SPECTRUM PER SESSION)
CONVERT AVERAGE SKIN SPECTRUM TO ABSORBANCE (USE ONLY 1ST. REFERENCE)
PERFORM LOF ON AVG. SPECTRUM
RECORDS NOT PASSING LOF ARE DISREGARDED AND ARE NOT USED IN FURTHER PROCESSING
DID THE AVG. SPECTRUM PASS LOF ?
NO
A
YES
C

FIG. 6A2

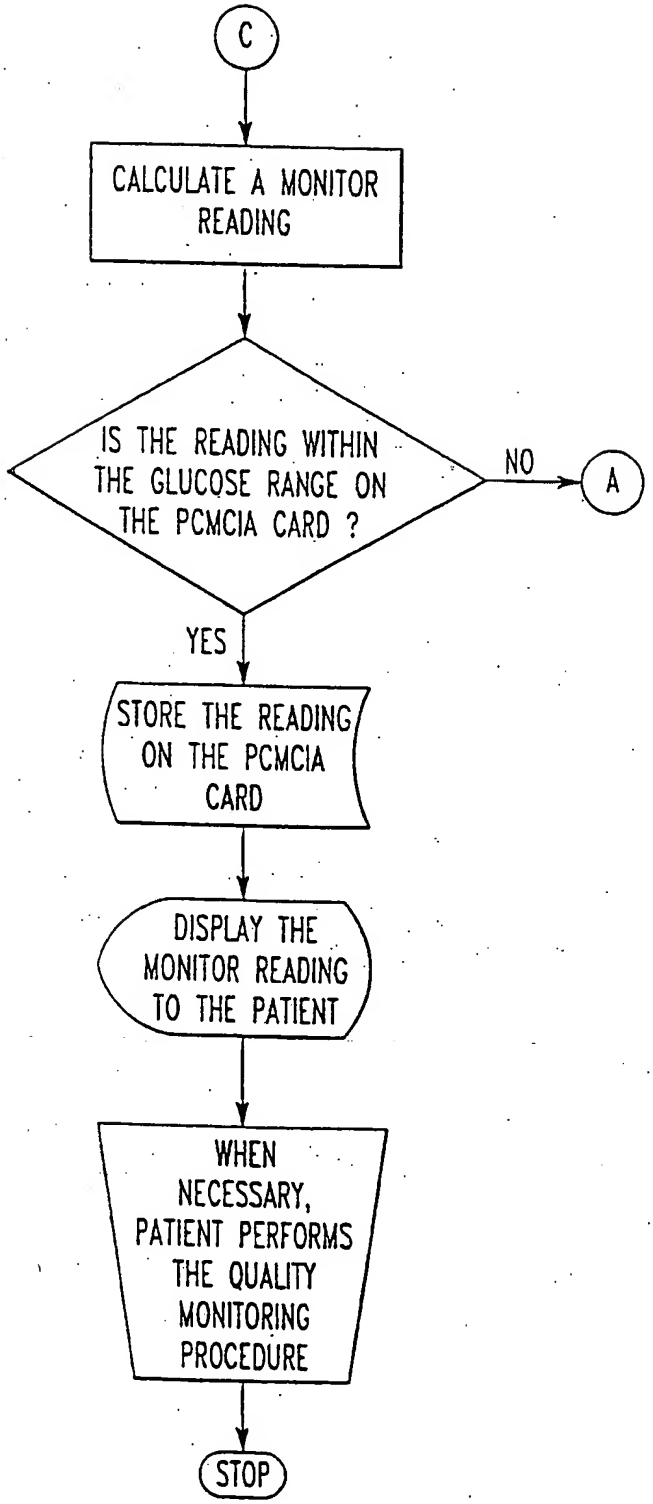

FIG. 6B1

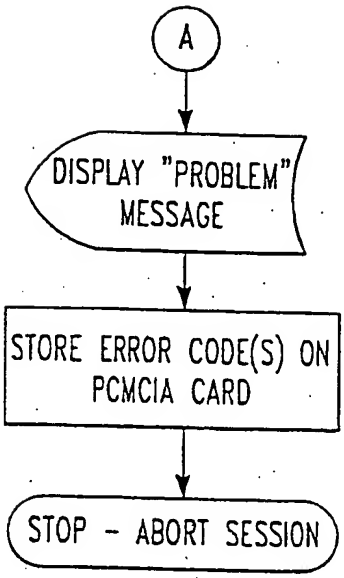

FIG. 6B2

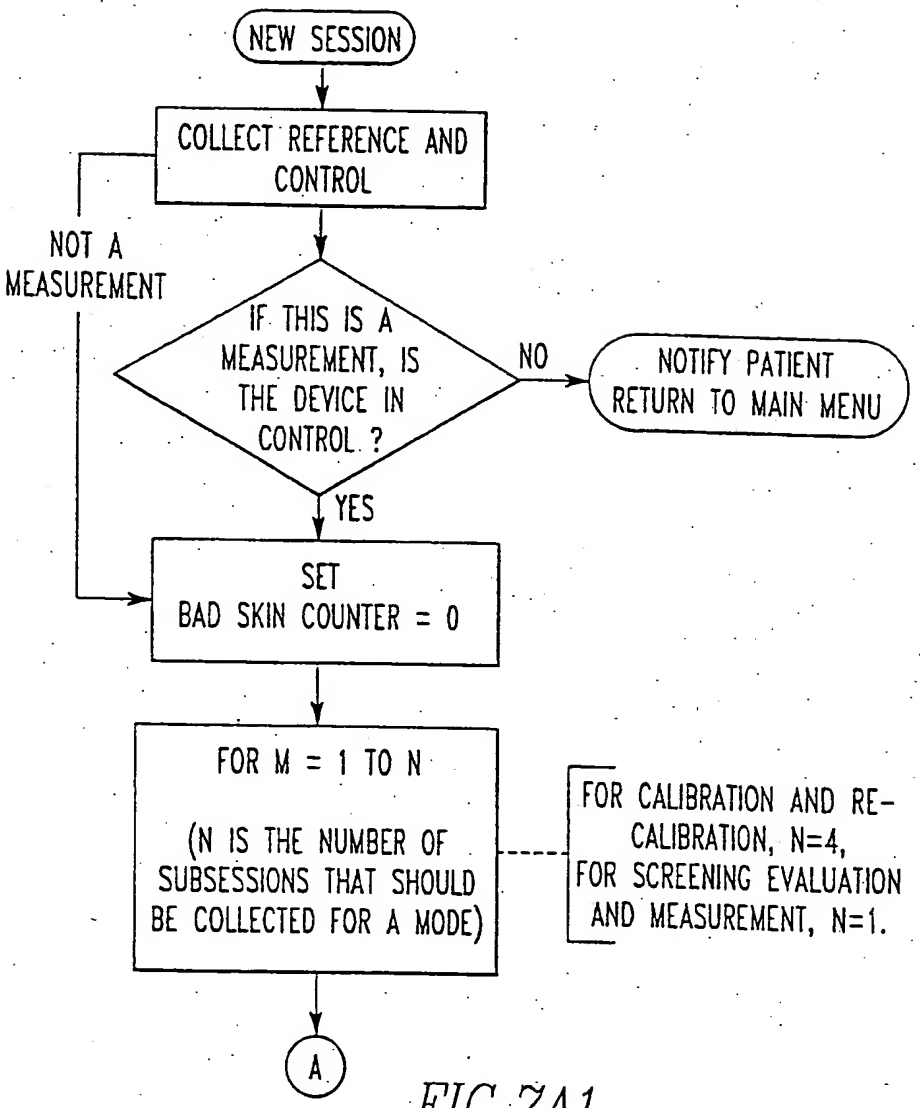
NEW SESSION
COLLECT REFERENCE AND CONTROL
NOT A MEASUREMENT
IF THIS IS A MEASUREMENT, IS THE DEVICE IN CONTROL ?
NO
NOTIFY PATIENT RETURN TO MAIN MENU
YES
SET BAD SKIN COUNTER = 0
FOR M = 1 TO N
(N IS THE NUMBER OF SUBSESSIONS THAT SHOULD BE COLLECTED FOR A MODE)
FOR CALIBRATION AND RE-CALIBRATION, N=4, FOR SCREENING EVALUATION AND MEASUREMENT, N=1.
A

FIG. 7A1

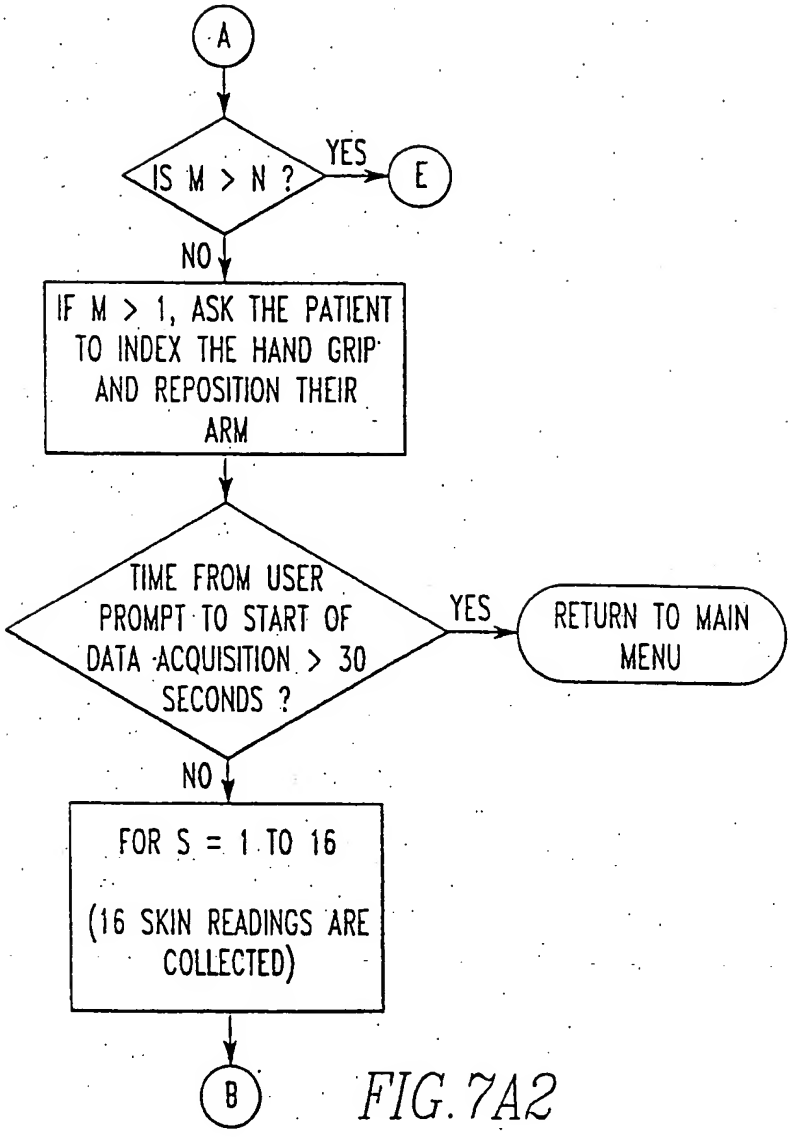
A
IS M > N ?
YES
E
NO
IF M > 1, ASK THE PATIENT TO INDEX THE HAND GRIP AND REPOSITION THEIR ARM
TIME FROM USER PROMPT TO START OF DATA ACQUISITION > 30 SECONDS ?
YES
RETURN TO MAIN MENU
NO
FOR S = 1 TO 16
(16 SKIN READINGS ARE COLLECTED)
B

FIG. 7A2

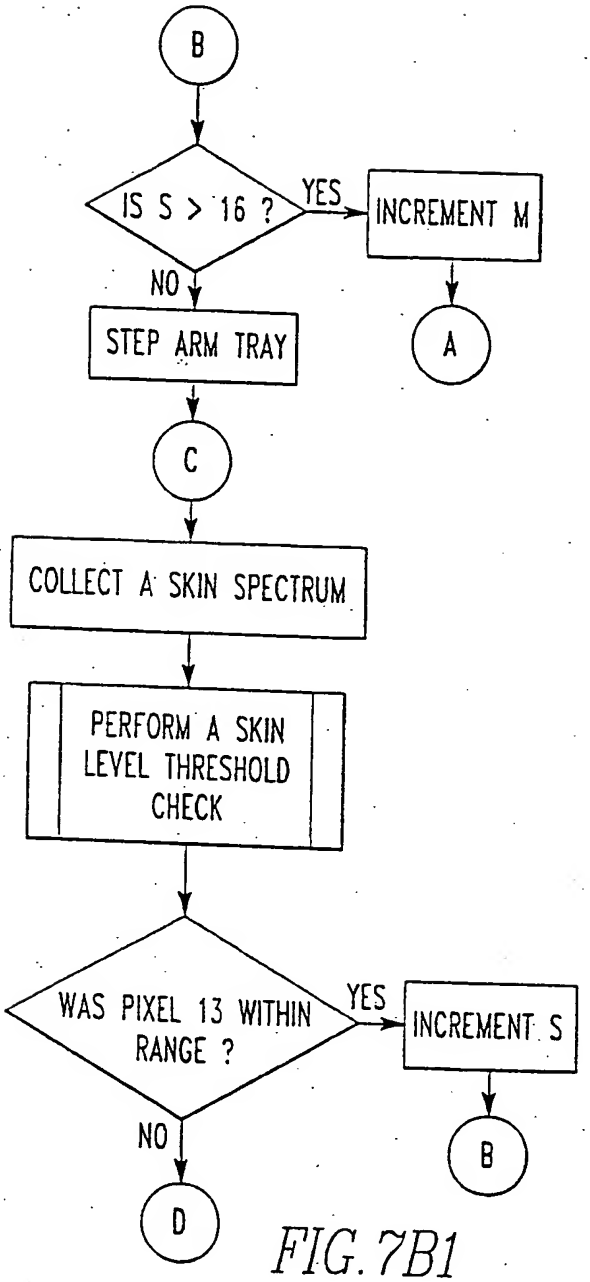

FIG. 7B1

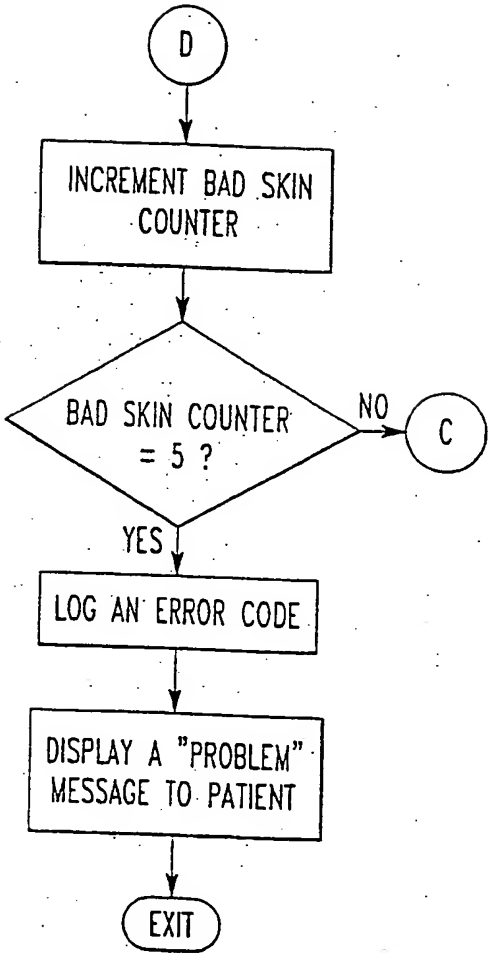

FIG. 7B2

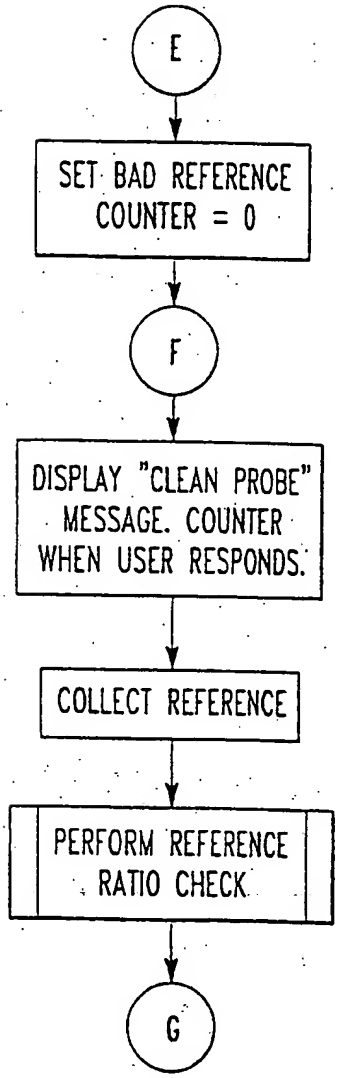
E
SET BAD REFERENCE COUNTER = 0
F
DISPLAY "CLEAN PROBE" MESSAGE. COUNTER WHEN USER RESPONDS.
COLLECT REFERENCE
PERFORM REFERENCE RATIO CHECK
G

FIG. 7C1

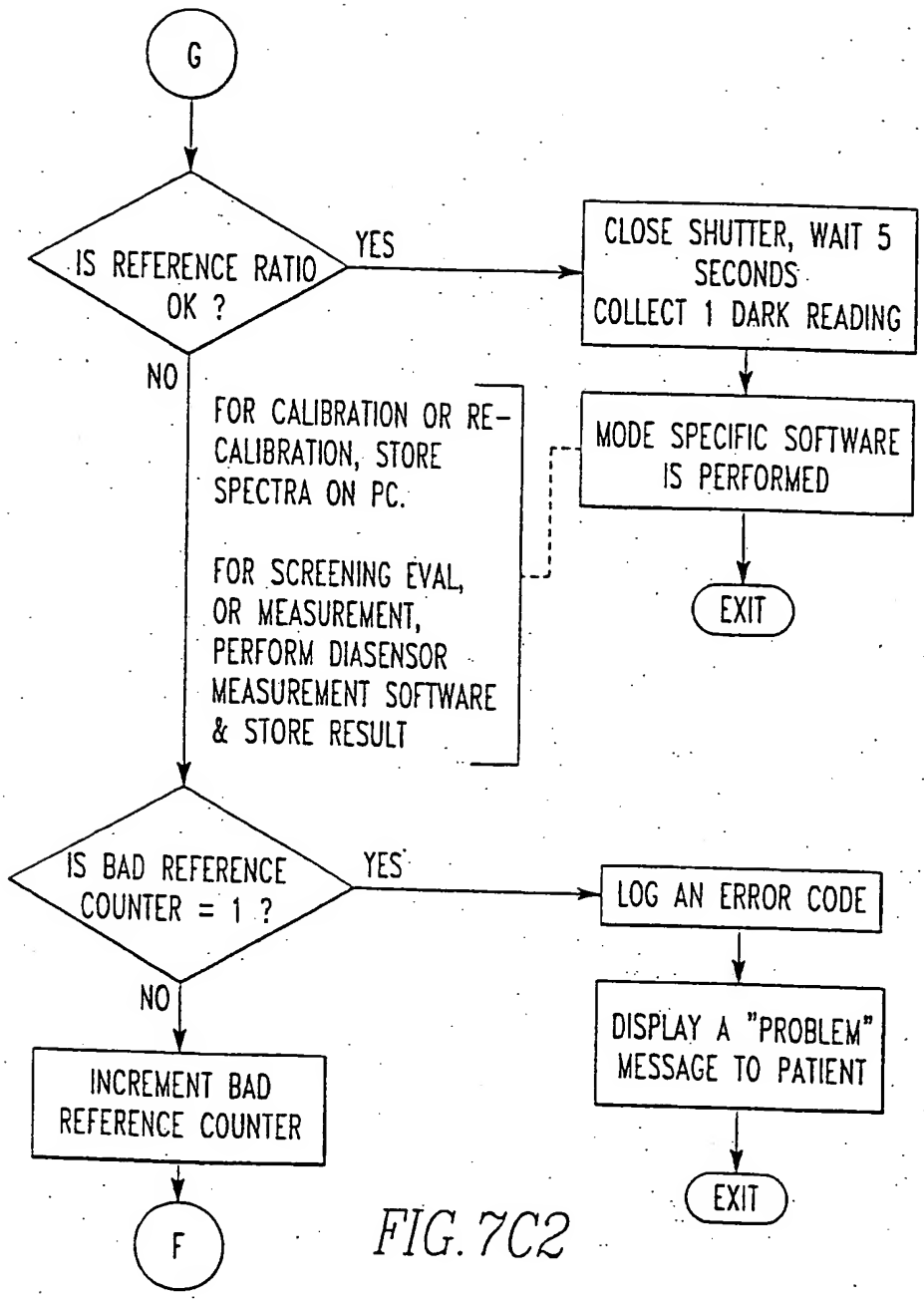
G
IS REFERENCE RATIO OK ?
YES
NO
CLOSE SHUTTER, WAIT 5 SECONDS COLLECT 1 DARK READING
MODE SPECIFIC SOFTWARE IS PERFORMED
EXIT
FOR CALIBRATION OR RE-CALIBRATION, STORE SPECTRA ON PC.
FOR SCREENING EVAL, OR MEASUREMENT, PERFORM DIASENSOR MEASUREMENT SOFTWARE & STORE RESULT
IS BAD REFERENCE COUNTER = 1 ?
YES
NO
LOG AN ERROR CODE
DISPLAY A "PROBLEM" MESSAGE TO PATIENT
EXIT
INCREMENT BAD REFERENCE COUNTER
F

FIG. 7C2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/03762

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61B 5/00
US CL :600/365
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 600/365, 316, 322, 326, 347, 368, 475

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,341,805 A (STAVRIDI ET AL) 30 August 1994.	1-21
A	US 5,329,931 A (CLAUSON ET AL) 19 July 1994.	1-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
18 JUNE 1998

Date of mailing of the international search report
08 JUL 1998

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